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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1.	Your Reference	HKQ/PU3517
2.	Patent application number *(The Patent office will fill in this part)*	9920872.0
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 0NN, G
	Patents ADP number *(if you know it)*	473587002
	If the applicant is a corporate body, give the country/state of its corporation	
4	Title of the invention	BENZOPHENONES AS INHIBITORS OF REVERSE TRANSCRIPTASE
5	Name of your agent *(if you know one)*	HELEN K. QUILLIN (SEE CONTINUATION SHEET)
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXO WELLCOME PLC GLAXO WELLCOME HOUSE, BERKELEY AVENUE GREENFORD, MIDDLESEX UB6 ONN, GB
	Patents ADP number *(if you know it)*	6470579001

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6.	If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day / month / year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.*	YES

BENZOPHENONES AS INHIBITORS OF REVERSE TRANSCRIPTASE

Background of the Invention

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), in addition to the nucleoside reverse transcriptase inhibitors gained a definitve place in the treament of HIV-1 infections. The NNRTIs interact with a specific site of HIV-1 reverse transcriptase that is closely associated with, but distinct from, the NRTI binding site. NNRTIs, however, are notorius for rapidly eliciting resistance due to mutations of the amino acids surrounding the NNRTI-binding site (E. De Clercq, *Il Famaco* 54, 26-45, 1999). Failure of long-term efficacy of NNRTIs is often associated with the emergence of drug-resistant virus strains (J. Balzarini, *Biochemical Pharmacology*, Vol 58, 1-27, 1999). Moreover, the mutations that appear in the reverse transcriptase enzyme frequently result in a decreased sensitivity to other reverse transcriptase inhibitors, which results in cross-resistance.

JP 59181246 disclosed certain benzophenones useful as anticancer agents. Certain benzophenone derivatives as inhibitors of HIV-1 reverse transriptase were disclosed in Wyatt et al. (J. Med. Chem. 38:1657-1665, 1995). However, these compounds were primarily active against wild-type HIV-1 reverse transcriptase, rapidly induced resistant virus, and were inactive against a common resistant strain.

We have now discovered that the compounds of the present invention are useful as inhibitors of both wild type and mutant variants of HIV reverse transcriptase.

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally subsituted with one or more subsitutents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

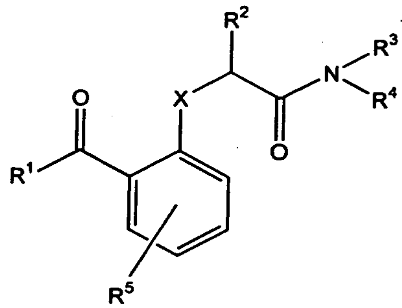
R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

R^{10} is C_{1-8}alkyl;

In another aspect of the present invention compounds of formula (IA) are disclosed:



(IA)

wherein:

X is C, O, or N;

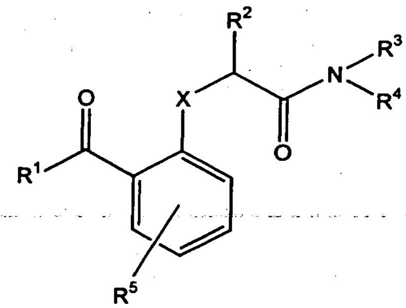
R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 is hydrogen;



(IB)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$;

R^{10} is C_{1-8}alkyl;

R^4 C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $-C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

$R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (IC) are those wherein X is O.

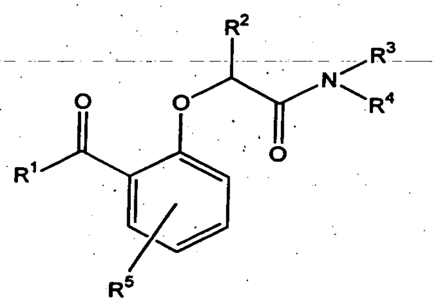
More preferred compounds of formula (IC) are those wherein X is O; R^1 is heterocycle, optionally substituted with -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-OR^{11}$, and heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo; and R^5 is halogen.

or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (ID are those wherein X is O.

More preferred compounds of formula (ID) are those wherein X is O; R^1 is heterocycle; R^2 and R^3 are hydrogen; R^4 is heterocycle; and R^5 is halogen.

In a further aspect of the present invention there is provided compounds of formula (II):



(II)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

$-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally subsituted with one or more subsitutents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $-C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2$, $-S(O)_2NR^8R^9$, $-NR^8R^9$ and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

Preferred compounds of the present invention include:

2-[2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-imidazol-1-yl)phenyl]acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-1,2,4-triazol-1-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-morpholinyl)phenyl]acetamide;

N-[4-(aminosulfonyl)phenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-methyl-1-piperazinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(hydroxymethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(methylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1,1-dioxo-1lambda~6~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(4-morpholinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(dimethylamino)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(4-chloro-2-{[5-(2-pyridinyl)-2-thienyl]carbonyl}phenoxy)-N-phenylacetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(2-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(2-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-{4-chloro-2-[(5-methyl-3-isoxazolyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-(1,3-benzothiazol-6-yl)-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(2-methyl-1,3-benzothiazol-5-yl)acetamide

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(methylsulfonyl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-cyclopentylethynyl)benzoyl]phenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-phenylethynyl)benzoyl]phenoxy}acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone

Compounds of the present invention that are advantageous are those wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl, in addition to one or more other substituents as defined above.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain alkyl group with at least one carbon-carbon double bond. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutyenyl, pentenyl, hexenyl, hexadienyl and the like.

The term "alkynyl" refers to hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "aryl," alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "heterocycle" or "heterocyclic" as used herein, refers to a 3-to 7- membered monocyclic heterocyclic ring or 8-to 11- membered bicyclic heterocyclic ring which is

infection has become latent. The term “prophylactically effective amount” refers to an amount effective in preventing a virus infection, for example an HIV infection, or preventing the occurrence of symptoms of such an infection, in a patient. As used herein, the term “patient” refers to a mammal, including a human.

The term “pharmaceutically acceptable carrier or adjuvant” refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

As used herein, the compounds according to the invention are defined to include pharmaceutically acceptable derivatives thereof. A “pharmaceutically acceptable derivative” means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

In a further aspect of the invention there are provided the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections such as an HIV infection. Compounds according to the invention have been shown to be active against HIV infections, although these compounds may be active against HBV infections as well.

The compounds according to the invention are particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment extends to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

According to a particular embodiment of the present invetion, there is provided a method of treatment of HIV mutant viruses that exhibit NNRTI drug resistance by administering a thereapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable derivative thereof to a mammal, in particular a human. In particular, the compounds of the present invention may be used to treat wild-type HIV-1 as well as several resistance mutations, for example, K103N, L1001, or Y181C.

According to another aspect, the present invention provides a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. According to a particular embodiment of this aspect of the invention, the viral infection is a retorviral infection, in particular an HIV infection. A further aspect of the invention includes a method for the treatment or prevention of the symptoms or effects of an HBV infection.

The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

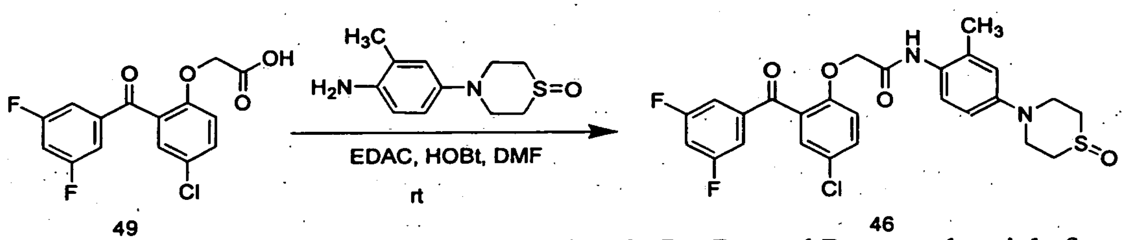
2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as indinavir, ritonavir, nelfinavir, amprenavir, oxathiolane nucleoside analogues such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (BI-RG-587), loviride (α -APA) and delavuridine (BHAP), and phosphonoformic acid, and 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266), and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

More preferably the combination therapy involves the administration of one of the above mentioned agents and a compound within one of the preferred or particularly preferred sub-groups within formulae (I) – (III) (including IA, IB, IC and ID) as described above. Most preferably the combination therapy involves the joint use of one of the above named agents together with one of the compounds of the present invention specifically named herein.

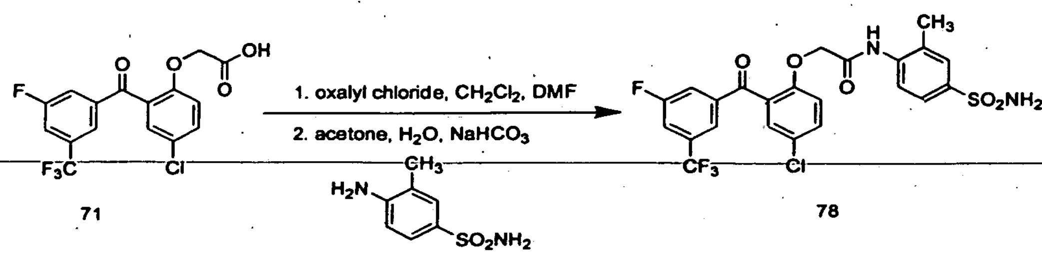
0 °C to 150 °C, most preferably at ambient temperatures. For example, carboxylic acid **49** (Scheme I) is allowed to react with amine **399** in DMF and in the presence of EDAC and HOBt at ambient temperature to provide compound **46**.

Scheme I



Alternatively, compounds of formula IV, wherein R_1, R_2, and R_5 are as hereinbefore defined, can first be converted to the corresponding acid chloride which is then allowed to react with compounds of formula V, wherein R_3 and R_4 are as hereinbefore defined, to afford compounds of (I). The preparation of the desired acid chloride can be accomplished by methods well-known in the art. The carboxylic acids can be allowed to react with a suitable dehydrating agent such as thionyl chloride or more preferably oxalyl chloride. These reactions are typically performed in an aprotic solvent such as acetonitrile or pyridine or a chlorinated solvent such as chloroform or more preferably dichloromethane. The corresponding acid chlorides are not typically isolated in pure form, but instead are allowed to react directly with compounds of formula V. Most often, reactions of the acid chlorides are performed in an aprotic solvent such as acetonitrile or chloroform, or more preferably in acetone. In addition, the presence of a compound capable of acting as a base such as triethylamine or pyridine, or more preferably sodium bicarbonate, is required in order to obtain sufficient yields of the coupling products. When inorganic bases such as sodium bicarbonate are used, the addition of a small amount of water to the reaction mixture promotes an efficient coupling reaction. For example, carboxylic acid **71** (Scheme II) is allowed to react with oxalyl chloride in dichloromethane and in the presence of a catalytic amount of DMF to afford the corresponding acid chloride. The acid chloride is then allowed to react with amine **466** in a mixture of acetone and water and in the presence of an excess of sodium bicarbonate to provide compound **78**

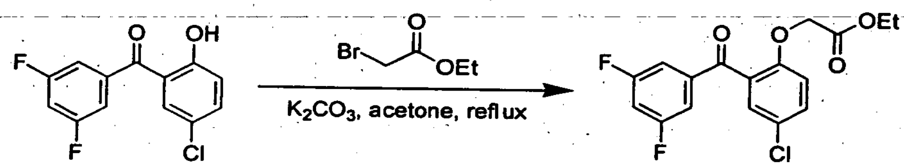
Scheme II



halogen, preferably chlorine or bromine, or a methanesulfonate or para-toluenesulfonate ester. Typically, the reactions are performed in an aprotic solvent such as acetonitrile, DMF, or more preferably acetone, and temperatures ranging from 40 °C to 100 °C. In addition, the presence of an excess of a base such as triethylamine, pyridine, or more preferably potassium carbonate, is usually required for efficient reaction. For example, phenol **47** (Scheme IV) is allowed to react with ethyl bromoacetate in refluxing acetone and in the presence of potassium carbonate to afford ester **48.**

Compounds of formula VII are either commercially available or can be prepared using literature methods that are known in the art.

Scheme IV

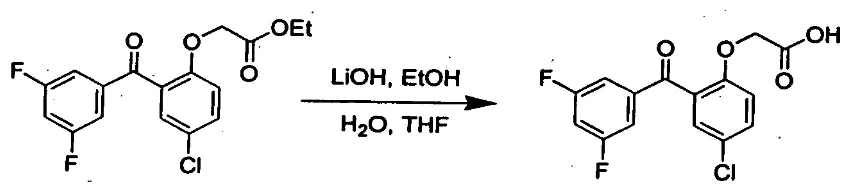


47 48

Compounds of formula IV, in which R_1, R_2 and R_5 are as hereinbefore defined and R_6 is hydrogen can be prepared from compounds of formula IV in which R_1, R_2 and R_5 are as hereinbefore defined and R_6 is C_{1-6}alkyl, by reaction with aqueous base or other suitable methods known in the art. A variety of inorganic bases can be used to affect the saponification of the esters of formula IV, such as sodium carbonate, sodium hydroxide or more preferably lithium hydroxide. Typically, these reactions are performed in water in addition to a solvent that is miscible with water and is capable of dissolving the compounds of formula IV such as tetrahydrofuran, methyl alcohol or ethyl alcohol.

For example, ester **48** (Scheme V) is allowed to react with lithium hydroxide in a mixture of THF, water, and ethanol to afford carboxylic acid **49.**

Scheme V

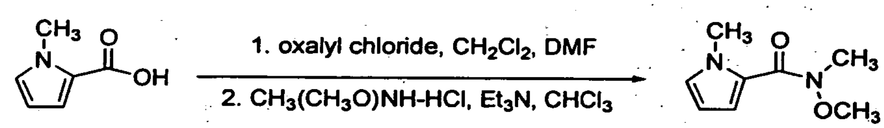


48 49

Compounds of formula IX, in which R_5 is as hereinbefore defined, R_7 is methyl and R_9 is either bromine or iodine are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula X, in which R_1 is as hereinbefore defined and R_{10} is N,O-dimethylhydroxylamino, can be prepared from compounds of formula X in which R_{10} is a suitable leaving group, preferably chlorine, by reaction with N,O-dimethylhydroxylamine in an aprotic solvent, preferably acetonitrile, chloroform or dichloromethane, and in the presence of a base, preferably triethylamine. Compounds of formula X in which R_{10} is chlorine can be prepared from compounds of formula X, in which R_{10} is hydroxy, using literature methods known in the art, such as reaction with oxalyl chloride in an aprotic solvent, preferably dichloromethane or chloroform and in the presence of a catalytic amount of DMF. For example, 1-methyl-2-pyrrolecarboxylic acid (Scheme VII) in dichloromethane is allowed to react with excess oxalyl chloride in the presence of a catalytic amount of DMF. The resulting acid chloride is not isolated in pure form, but instead is allowed to react with N,O-dimethylhydroxylamine in chloroform and in the presence of triethylamine, to afford amide **14**.

Scheme VII

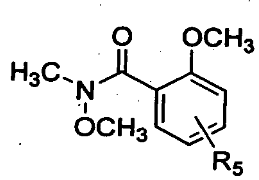


14

Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl can be prepared by reaction of compounds of formula IX with those of formula X, wherein R_1 and R_5 are as hereinbefore defined with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is N,O-dimethylhydroxylamino. Compounds of formula IX can be converted to a species in which R_9 is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R_{10} is N,O-dimethylhydroxylamino. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl

Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula IX with those of formula X, wherein R_1 and R_5 are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is hydrogen. Compounds of formula IX can be converted to a species in which R_9 is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R_{10} is hydrogen, to afford an intermediate alcohol. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0 °C to 100 °C, preferably ambient temperature. The preparation of compounds of formula IX, in which R_9 is a magnesium halide, can be accomplished by literature methods known in the art. Typically, a compound of formula IX, in which R_9 is either bromine or iodine, is allowed to react with elemental magnesium, in an aprotic, ethereal solvent. The intermediate alcohol is then allowed to react with an agent capable of oxidizing it to the desired ketone, preferably manganese (IV) oxide, in an aprotic solvent, preferably dichloromethane or chloroform, and at ambient temperature.

Lastly, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula XII, in which R_5 is as hereinbefore defined, with compounds of formula XIII, in which R_1 is as hereinbefore defined, and R_{11} is a halogen, preferably bromine or iodine, with the further stipulation that R_1 and R_5 are chemically compatible with subsequent chemical steps.

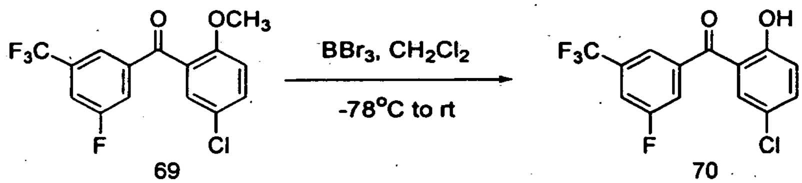


XII

$R_1{-}R_{11}$

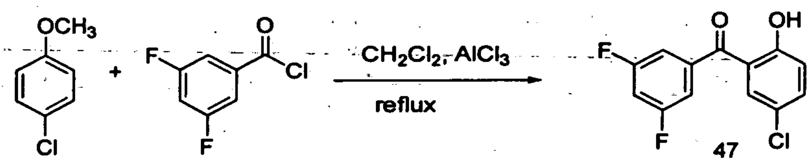
XIII

Typically, compounds of formula XIII, in which R_{11} is a halogen, preferably iodine or bromine, are treated with an agent capable of effecting a halogen-metal exchange reaction, preferably n-butyl lithium, in an ethereal solvent, preferably diethyl ether and at low temperature, preferably -78 °C.



Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined, and R_7 is hydrogen, can be prepared by reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, R_9 is hydrogen and R_7 is methyl, with compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, preferably chlorine, with the further stipulation that R_1 and R_5 are chemically compatible with the reaction conditions. These reactions, typically called Friedel-Craft acylations, are performed in an aprotic solvent such as nitrobenzene, 1,2-dichloroethane, sulfolane, or more preferably dichloromethane, at temperatures ranging from 0 °C to 150 °C, preferably 35-60 °C. In addition, the use of a compound which is capable of acting as a Lewis acid, such as titanium (IV) chloride, tin (IV) chloride, or more preferably aluminum chloride is required. For example, 4-chloroanisole (Scheme X) is allowed to react with 3,5-difluorobenzoyl chloride in refluxing dichloromethane in the presence of aluminum chloride to afford ketone **47**.

Scheme X

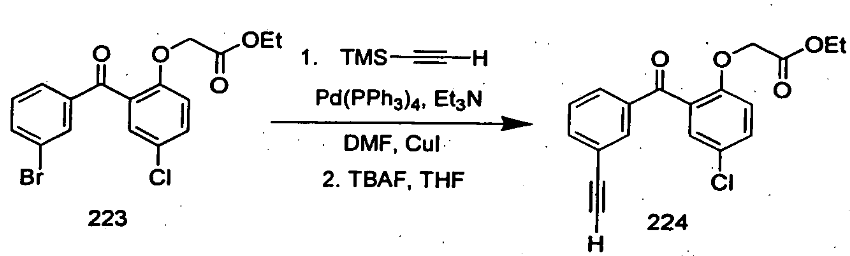


Compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, are either commercially available or can be prepared by literature methods. Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore described and R_7 is hydrogen, can prepared from the reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, and R_7 and R_9 are hydrogen, with compounds of formula X, in which R_1 in as hereinbefore defined and R_{10} is a halogen, preferably chlorine. These reactions, typically called Fries rearrangements, are performed in an aprotic solvent, such as nitrobenzene, sulfolane or chloroform and at temperatures ranging from 0 °C to 150 °C. In addition, the reaction typically requires the presence of a compound capable of acting as

palladium on carbon and Raney nickel. In addition, the presence of a reducing agent such as ammonium formate or pressurized hydrogen gas is required. These reactions are typically performed in a solvent capable of dissolving the olefinic substrate such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14}heterocycle, substituted with C_{2-8} alkynyl groups, can be prepared from compounds of formula XIV, in which R_5 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxyl ester and R_{12} is a group capable of undergoing a palladium-catalyzed reaction, preferably iodine or bromine, by reaction with C_{2-8} alkynes. These reactions are typically performed in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, palladium dichloride bis(acetonitrile), or palladium acetate. The solvents for these reactions are typically aprotic solvents such as acetonitrile, or more preferably DMF. The reactions are usually performed at temperatures ranging from ambient temperature to 130 °C, preferably 50-90 °C. In addition, the presence of a base such as potassium or sodium carbonate, or triethylamine, is usually required. Furthermore, reactions of some substrates may require the addition of a compound which is capable of stabilizing any intermediate palladium species. These compounds are most often triaryl arsine or phosphine derivatives, such as triphenylphosphine, or tri-ortho-tolylphosphine. Lastly, these reactions require the presence of a catalytic amount of copper (I) iodide. For example, ester **223** (Scheme XI) is allowed to react with trimethylsilylacetylene, in the presence of tertakis(triphenylphosphine)palladium, triethylamine and copper (I) iodide, to afford the intermediate trimethylsilyl-protected product. Treatment of the intermediate with tetrabutylammonium fluoride in THF provides compound **224**

Scheme IX



The C_{2-8} alkenes used in these reactions are either commercially available or can be prepared by literature methods familiar to those skilled in the art.

functional group. Among these agents are copper (I) cyanide or a palladium catalyst in combination with an appropriate cyanide source such as potassium cyanide, sodium cyanide, or zinc cyanide. Among the palladium agents that can be employed for this transformation are tertrakis(triphenylphosphine)palladium, palladium acetate, or palladium dichloride bis(acetonitrile). These reactions are typically conducted in aprotic solvents such as acetonitrile, or more preferably DMF, and in the presence of phosphine ligand, such as triphenylphosphine, and at temperatures from 20 °C to 150 °C, preferably 80-85 °C.

Compounds of formula VI, in which R_1 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxy ester and R_5 is hydrogen, halogen, nitro, trifluoromethyl, C_{1-8} alkyl or alkoxy can be prepared from commercially available material using processes described herein or by literature methods familiar to those skilled in the art.

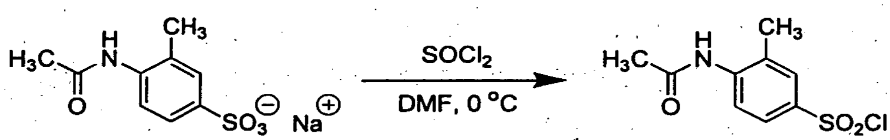
Compounds of formula VI, in which R_1 is as previously described, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is amino, can be prepared from compounds of formula VI in which R_5 is nitro by reaction with agents or a combination of agents capable of reducing a nitro group to an amino functionality. Among these combination of agents are a metal containing compound, such as elemental iron, palladium or Raney nickel and a reducing agent, such as ammonium formate, formic acid, hydrochloric acid or pressurized hydrogen gas. These reactions are typically performed in a solvent such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol and at temperatures ranging from 20 °C to 100 °C, preferably ambient temperature.

Compounds of formula VI in which R_1 is as hereinbefore defined, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is C_{1-8} alkylamino can be prepared from compounds of formula VI in which R_5 is amino, by reaction with agents capable of selectively alkylating the amino group. Among these agents are alkyl halides, such as methyl iodide, alkylsulfonate esters or alkylaryl sulfonate esters. These reactions are typically performed in polar, aprotic solvents such as N-methylpyrrolidine or DMF and at temperatures ranging from ambient to 150 °C.

Compounds of formula V, in which R_3 and R_4, which may be the same or different, are hydrogen, hydroxy, C_{1-8}alkyl, heterocycle, C_{6-14}arylheterocycle or C_{6-14}aryl are commercially available or can be prepared by literature methods familiar to those skilled in the art.

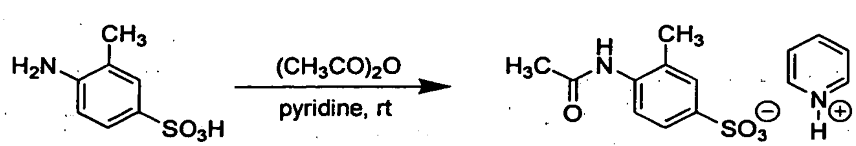
Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2Cl$, can be prepared from compounds of formula XV, in which R_{16} is $-SO_3H$ or a salt thereof, by reaction with an agent capable of converting a sulfonic acid or a salt thereof to a sulfonyl chloride. Among the agents that are capable of affecting this transformation are phosphorous oxychloride ($POCl_3$), or thionyl chloride. These reactions are conducted in an aprotic solvent such as DMF, and at temperatures from -10 °C to 100 °C, preferably 0 °C. For example, compound X (Scheme XIV) is allowed to react with thionyl chloride in DMF at 0 °C to provide sulfonyl chloride X.

Scheme XIV



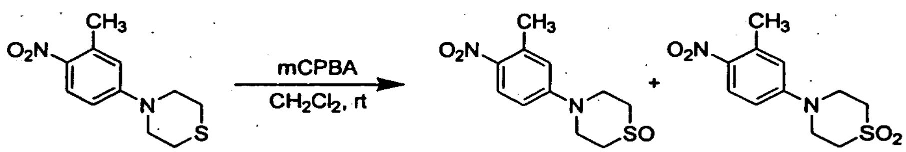
Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_3H$ or a salt thereof, can be prepared from compounds of formula XV, in which R_{14} is hydrogen, by reaction with an agent capable of selectively protecting the amino group. Among the reagents that are capable of affecting this transformation are trifluoroacetic anhydride, acetyl chloride, or more preferably acetic anhydride. These reactions are conducted in an aprotic solvent, such as acetonitrile, dichloromethane, chloroform, or more preferably pyridine, and at temperatures from 0 °C to 100 °C, preferably ambient temperatures. For example, compound X (Scheme XV) is allowed to react with acetic anhydride in pyridine at ambient temperature to provide compound X.

Scheme XV



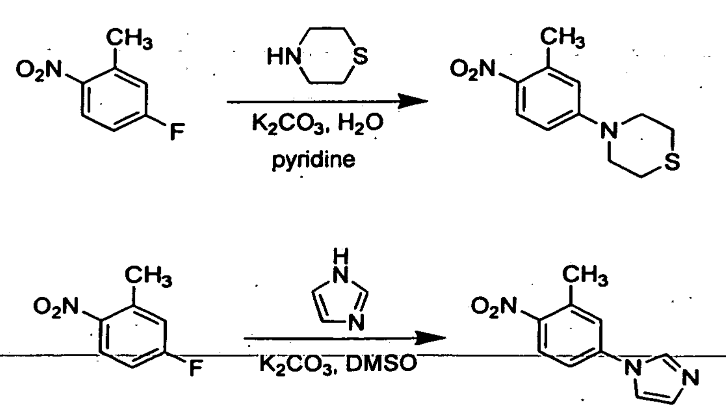
chloroperbenzoic acid (mCPBA), hydrogen peroxide, or oxone. These reactions are typically performed in solvents such as water, THF, acetonitrile, dichloromethane, methyl alcohol, ethyl alcohol, or a mixture thereof and at temperatures from 0 °C to 100 °C. For example, compound X (Scheme XVII) is allowed to react with MCPBA in chloroform at room temperature to provide both the sulfoxide X and the sulfone X.

Scheme XVII



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with -S, or -O can be prepared from compounds of formula XVI, in which R_{17} is or contains a suitable leaving group, such as a halide, preferably fluorine, chlorine, or bromine, by reaction with heterocyclic compounds capable of displacing the leaving group. Among the heterocycles that can affect this transformation are imidazole, 1,2,3-triazole, 1,2,4-triazole, morpholine, thiomorpholine, N-methylpiperazine, piperazine, and piperidine. These reactions are typically performed in an aprotic solvent such as dioxane, THF, dimethylsulfoxide or pyridine, and in the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate, and at temperatures from 0 °C to 150 °C, preferably 50-100 °C. Two such examples are shown below in Scheme XIX. In the first example, 5-fluoro-2-nitrotoluene is allowed to react with thiomorpholine in pyridine and water and in the presence of potassium carbonate to afford compound X. In the second example, 5-fluoro-2-nitrotoluene is allowed to react with imidazole in dimethylsulfoxide, in the presence of potassium carbonate, at 70 °C to provide compound X.

Scheme XIX

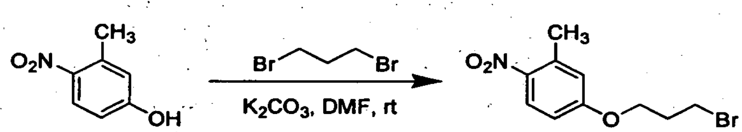


hereinbefore defined, or heterocycle, and R_{19} is a leaving group, preferably bromine or chlorine. These reactions are usually conducted in an aprotic solvent such as DMF, N-methylpyrrolidine, acetonitrile, or pyridine. In addition, the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate is usually required. For example, 4-nitro-3-methylphenol (Scheme XXI) is allowed to react with 1,3-dibromopropane in DMF and in the presence of potassium carbonate to afford compound X.

$$R_{19}-R_{18}$$

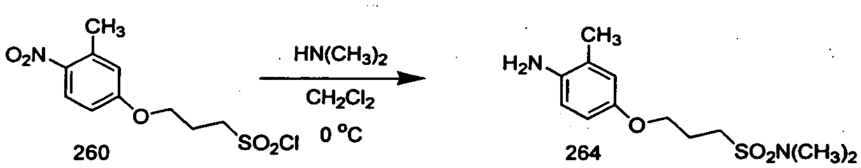
XVII

Scheme XXI



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8}alkyl substituted with $-SO_2NR_6R_7$, can be prepared from compounds of formula XVI, in which R_8 is C_{1-8}alkyl substituted with $-SO_2Cl$, by reaction with ammonia or an appropriate amine. These reactions are typically performed in aprotic solvents such as acetonitrile, or more preferably dichloromethane or chloroform. For example, sulfonyl chloride **260** (Scheme XXII) is allowed to react with dimethylamine in dichloromethane at 0 °C to provide sulfonamide **264**.

Scheme XXII

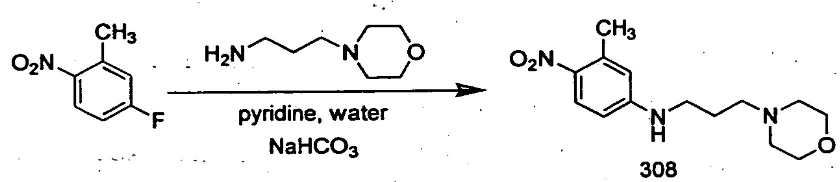


260 264

Compounds of formula XVI in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8}alkyl substituted with $-SO_2Cl$, can be prepared from compounds of formula XVI in which R_{17} is $-OR_8$ and R_8 is

solvents such as DMF, acetonitrile, dioxane, water, pyridine, or a mixture thereof, and in the presence of a base such as sodium or potassium carbonate, or more preferably sodium bicarbonate. For example, 5-fluoro-2-nitrotoluene (Scheme XXV) is allowed to react with 4-(3-aminopropyl)morpholine in pyridine and water and in the presence of sodium bicarbonate to provide compound **308.**

Scheme XXV



The desired amines of formula HNR_6R_7 are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula V, in which R_3 is hydrogen and R_4 is an aromatic heterocycle, are either commercially available or can be prepared using literature methods familiar to those skilled in the art.

A further object of the present invention features intermediates **7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433,** useful in the manufacture of the compounds of the present invention.

The compounds according to the invention, also referred to herein as the active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and the chosen active ingredient.

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day,

thereof and at least one further therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in *Pharmaceutical Research* 3 (6), 318 (1986).

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes a compound according to the invention or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

General Procedures:

General procedure I: Friedel-Crafts reaction of acid chlorides with 4-chloroanisole

Into a round-bottom flask equipped with a stir bar, a reflux condenser, and nitrogen on demand, were placed 4-chloroanisole (1-1.25 mmol/mmol of acid chloride), aluminum chloride ($AlCl_3$, 1-1.75 mmol/mmol of acid chloride) and CH_2Cl_2. To the resulting mixture was added the appropriate acid chloride at rt. When the addition was complete, the orange mixture was heated to reflux and was allowed to stir for 2-24 h. The mixture was allowed to cool to rt and was carefully poured onto ice water, giving a two-phase mixture which was stirred at rt for 30 min to 2 h. It was then poured into a separatory funnel containing water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples for details regarding additional purification.

General procedure II: Alkylation of phenols with ethyl bromoacetate

Into a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed the appropriate phenol, potassium carbonate (2-10 mmol/mmol of phenol), ethyl bromoacetate (1-1.5 mmol/mmol of phenol) and acetone (1-10 mL/mmol of

General Procedure V: Synthesis of acid chlorides from carboxylic acids using oxalyl chloride

Into a round-bottom flask were placed the appropriate carboxylic acid, methylene chloride (CH_2Cl_2, 1-10 mL/mmol acid), and N,N-dimethylformamide (1-10 drops). The mixture was cooled to 0 °C and oxalyl chloride (1-2 mmol/mmol acid) was added dropwise, after which time the mixture was allowed to warm to rt and stir for 1-24 h. The solvents were then removed under reduced pressure and the remaining residue was dried in vacuo. In most cases, the acid chlorides were used immediately used in subsequent reactions with no further purification.

General procedure VI: Coupling of acid chlorides to aromatic amines using sodium bicarbonate

Into a round-bottom flask were placed the appropriate aromatic amine, acetone (1-10 mL/mmol amine), sodium bicarbonate (2-10 mmol/mmol amine), and water (0.25-10 mL). The acid chloride was added as a solution in acetone (1-10 mL/mmol of acid chloride) in a dropwise manner and the reaction mixture was allowed to stir at rt for 1-24 h. When judged to be complete, the mixture was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples for details regarding further purification of the products.

General procedure VII: Synthesis of Weinreb amides from acid chlorides using N,O-dimethylhydroxylamine hydrochloride

Into a round bottom flask equipped with a stir bar and nitrogen on demand were placed the N,O-dimethylhydroxylamine (1-2 mmol/mmol acid chloride) and chloroform ($CHCl_3$, 1-10 mL/mmol acid chloride). The mixture was cooled to 0 °C and triethylamine (Et_3N, 1-5 mmol/mmol acid chloride) was added in one portion. The acid chloride was added and the reaction mixture was allowed to stir at 0 °C for 0.5-5 h, after which time was poured into a separatory funnel containing chloroform and water. The organics were collected, washed with water and brine, dried over $MgSO_4$, filtered and the solvents were removed under

dissolved, and washed with water. The resulting organics were dried over $MgSO_4$ and concentrated in vacuo and purified as descried in the individual cases.

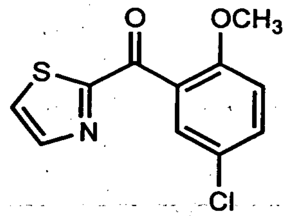
General Procedure XI. An amine (1-2.5 mmol/mmol benzene) was added dropwise via an addition funnel to a stirred suspension of a para-nitro halogenated benzene or toluene in pyridine (20-40 mmol/mmol benzene), sodium bicarbonate (1.5-4 mmol/mmol benzene), and water (0.2-5 mL/mmol benzene). The resulting suspension was refluxed (150 °C) for 1-7 days. The mixture was filtered and acetone (10-200 mL/mmol benzene) was added to the filtrate and brought to reflux. Water was added to the cloud point and the solution was cooled to rt. The precipitate was filtered and the resulting solid was washed with water and ether to afford the substituted product.

General Procedure XII. The appropriate nitro-benzene was added to a suspension of palladium on carbon (0.1-0.8 mmol /mmol benzene, 10% w/w), ethanol, THF, and methanol and the reaction vessel was evacuated and charged with nitrogen several times. After evacuating the reaction vessel under reduced pressure, it was charged with hydrogen (14-100 psi). The resulting suspension was stirred at rt for 0-72 h, filtered through a celite pad, and concentrated in vacuo to afford the appropriate aniline.

General procedure XIII. Into a round-bottom flask equipped with a stir bar, cooling bath, and nitrogen on demand were placed the appropriate carboxylic acid, hexachloroacetone (HCA, 0.5 mmol/mmol acid), and THF (1-10 mL/mmol acid) and the mixture was cooled -78 °C. Triphenylphosphine (PPh_3, 1 mmol/mmol acid) in THF (1-10 mL/mmol acid) was added to the mixture and stirred for 5-120 min. The appropriate aniline (1 mmol/mmol acid) in THF (1-10 mL/mmol acid) and pyridine (5-20 mmol/mmol acid) were added dropwise and the mixture was stirred -78 °C for 5-60 min. The cooling bath was removed and the mixture was stirred at rt for 1h to 14 d. The reaction mixture was concentrated in vacuo and purified as described in the individual cases.

General procedure XIV. Thionyl chloride (1-100 mmol/mmol acid) was added to a solution of the appropriate carboxylic acid in methylene chloride (1-100 ml/mmol acid) and the resulting solution was refluxed for 1-12 h under nitrogen. The mixture was concentrated in vacuo and placed under nitrogen to afford the appropriate acid chloride.

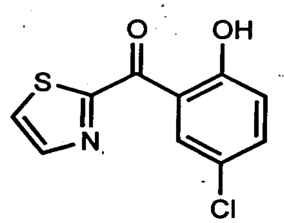
Step B:



3

2 (5.21 g, 20.6 mmol), manganese dioxide (17.66 g, 203.1 mmol) and methylene chloride (CH_2Cl_2, 75 mL) were combined under nitrogen and were allowed to stir at RT for 2.5 h. The mixture was filtered through a pad of celite, which was washed with several portions of CH_2Cl_2, and the solvent was removed under reduced pressure to provide a tan solid (4.96 g, 95%) which was used in subsequent reactions without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J= 3 Hz, 1H), 7.76 (d, J= 3 Hz, 1H), 7.63 (d, J= 3Hz, 1H), 7.49 (dd, J= 9, 3 Hz, 1H), 7.00 (d, J= 9 Hz, 1H), 3.82 (s, 3H).

Step C:

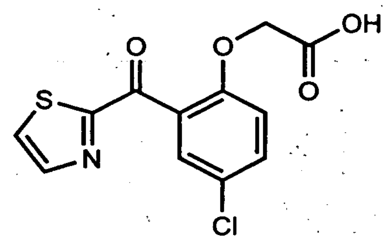


4

3 (4.96 g, 19.6 mmol), in CH_2Cl_2 (60 mL) was cooled to –78 °C and boron tribromide (100 mL of a 1.0 M solution in CH_2Cl_2, 100 mmol) was added via syringe over 30 min. The resulting purple solution was allowed to stir at –78 °C for 15 min, after which time it was allowed to slowly warm to RT. After 30 min at RT, the mixture was slowly poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. The mixture was then poured into a separatory funnel containing water and CH_2Cl_2. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, and the solvents were removed under reduced pressure. The product was isolated by flash chromatography using 7:3 hexane/ CH_2Cl_2 to provide a yellow solid (3.59 g, 76%). ^1H NMR ($CDCl_3$, 300 MHz)

Phenol **4** (2.31 g, 9.64 mmol), K_2CO_3 (6.95 g, 50.3 mmol), ethyl bromoacetate (1.1 mL, 1.7 g, 9.9 mmol) and acetone (150 mL) were used according to general procedure II. The product was used in the next reaction without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J= 3 Hz, 1H), 7.76 (d, J= 3 Hz, 1H), 7.66 (d, J= 3 Hz, 1H), 7.48 (dd, J= 9, 3 Hz, 1H), 6.93 (d, J= 9 Hz, 1H), 4.61 (s, 2H), 4,21 (q, J= 6 Hz, 2H), 1.26 (t, J= 6 Hz, 3H).

Step B:



7

Ester **6** (3.1 g, 9.6 mmol), THF (30 mL), water (10 mL), EtOH (10 mL) and LiOH (1.0 g, 23.8 mmol) were used according to general procedure III. The product was used in the next reaction without any further purification. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 8.30 (d, J = 3Hz, 1H), 8.15 (d, J= 3 Hz, 1H), 7.63 (d, J = 3 Hz, 1H), 7.57 (dd, J= 9, 3 Hz, 1H), 7.05 (d, J= 9 Hz, 1H), 4.45 (s, 2H).

Step C:

Carboxylic acid **7** (0.1 g, 0.33 mmol), HOBt (0.05 g, 0.4 mmol), EDAC (0.09 g, 0.46 mmol), Et_3N (0.1 mL, 0.07 g, 0.72 mmol), DMF (6 mL) and 5-aminoindazole (0.05 g, 0.35 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2: CH_3OH as eluant to provide 5 as a tan solid (0.03 g, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (s, 1H), 8.46 (s, 1H), 8.21 (s, 1H), 8.05 (m, 2H), 7.77 (m, 3H), 7.54 (m, 1H), 6.99 (d, J= 8 Hz, 2H), 4.74 (s, 2H).

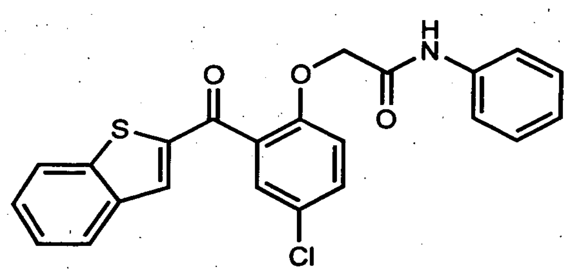
<u>**Example 3:**</u>

2-Benzofurancarboxylic acid (2.51 g, 15.48 mmol), CH_2Cl_2 (50 mL), DMF (4 drops), and oxalyl chloride (1.5 mL, 2.18 g, 17.19 mmol) were used to prepare the corresponding acid chloride according to general procedure V. The acid chloride was used immediately in combination with 4-chloroanisole (2.16 g, 15.15 mmol), $AlCl_3$ (3.01 g, 22.57 mmol) and CH_2Cl_2 (50 mL) according to general procedure I. Compound **10** was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide 10 as a yellow solid (2.39 g, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.05 (s, 1H), 8.48 (d, J= 3Hz, 1H), 7.82 (d, J= 9 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J= 9 Hz, 1H), 7.56 (m, 2H), 7.42 (t, J= 7.5 Hz, 1H), 7.09 (d, J= 9 Hz, 1H).

Step B:

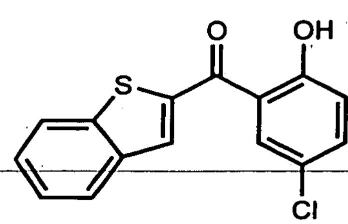
Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol **10** (0.14 g, 0.51 mmol), 2-chloroacetanilide (0.10 g, 0.59 mmol), K_2CO_3 (0.50 g, 3.62 mmol) and acetone (10 mL). The mixture was heated to reflux for 16 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave orange oil. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate as eluant to provide **9** as a white solid (0.12 g, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.33 (s, 1H), 7.75 (m, 5H), 7.61 (m, 3H), 7.39 (m, 3H), 7.15 (m, 2H), 4.77 (s, 2H).

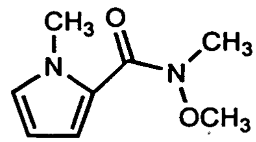
__Example 5__



11

Step A:



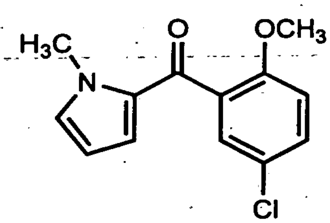


Step A:

14

1-Methyl-2-pyrrolecarboxylic acid (4.75 g, 37.96 mmol), CH_2Cl_2 (100 mL), DMF (0.5 mL) and oxalyl chloride (3.6 mL, 5.24 g, 41.27 mmol) were used according to general procedure V. Into a separate flask were placed N,O-dimethylhydroxylamine hydrochloride (4.45 g, 45.62 mmol), Et_3N (26 mL, 19 g, 187 mmol) and chloroform (100 mL). The resulting solution was cooled to 0 °C and the acid chloride (in 20 mL of chloroform) was added dropwise. The resulting mixture was allowed to stir at 0 °C for an additional 1 h, after which time it was allowed to warm to RT. The mixture was then poured into a separatory funnel containing chloroform and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a brown oil which was used in subsequent reactions with no further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (m, 1H), 6.78 (m, 1H), 6.15 (m, 1H), 3.94 (s, 3H), 3.73 (s, 3H), 3.36 (s, 3H).

Step B:

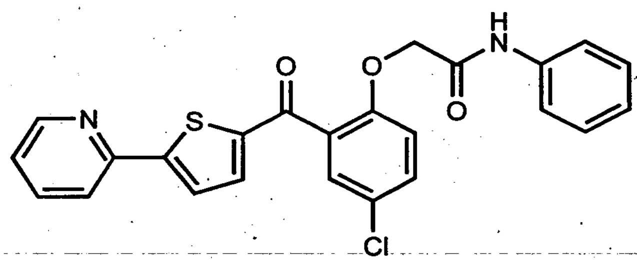


15

To a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.97 g, 26.95 mmol) and THF (75 mL). The resulting solution was cooled to –78 °C and n-butyl lithium (19.5 mL of a 1.6 M solution in hexane, 31.2 mmol) was added via syringe. The resulting solution was allowed to stir at –78 °C for 30 min and amide **14** (4.2 g, 24.97 mmol in 15 mL THF), was added via syringe. The mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with

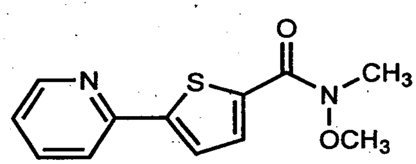
MHz) δ 9.69 (s, 1H), 7.81 (d, J= 9 Hz, 2H), 7.54 (d, J= 3 Hz, 1H), 7.47 (dd, J= 6, 3 Hz, 1H), 7.38 (t, J= 6Hz, 2H), 7.16 (t, J= 6 Hz, 1H), 7.03 (m, 2H), 6.75 (m, 1H), 6.23 (m, 1H), 4.75 (s, 2H), 4.17 (s, 3H).

Example 7



17

Step A:



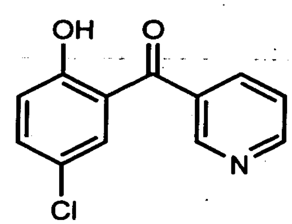
18

5-(2-pyridyl)thiophene-2-carboxylic acid (2.62 g, 12.77 mmol), oxalyl chloride (1.4 mL, 2.04 g, 16.05 mmol), DMF (0.25 mL) and CH_2Cl_2 (25 mL) were used according to general procedure V. The acid chloride was used immediately in the next step without any further purification. Into a separate flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (1.63 g, 16.71 mmol), Et_3N (9 mL, 6.53 g, 64.57 mmol) and CH_2Cl_2 (25 mL). The resulting solution was cooled to 0 °C, and the acid chloride (in 10 mL of CH_2Cl_2) was added dropwise. When the addition was complete, the mixture was allowed to stir at 0 °C for an additional 30 min, and then was allowed to warm to rt and stir for an additional 1h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure leaving a white solid (2.69 g, 85%). The product was used in subsequent steps without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, J

and boron tribromide (20 mL of a 1.0 M solution in CH_2Cl_2, 20 mmol) was added via syringe. The resulting dark red mixture was allowed to stir at –78 °C for 1 h and it was then allowed to warm to rt and stir for an additional 1 h. The mixture was carefully poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a tan solid (1.32 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.55 (s, 1H), 8.70 (d, J= 6 Hz, 1H), 8.00 (d, J= 3 Hz, 1H), 7.82 (m, 3H), 7.75 (d, J= 3Hz, 1H), 7.51 (dd, J= 9, 3 Hz, 1H), 7.34 (m, 1H), 7.08 (d, J= 9 Hz, 1H).

Step D:

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed phenol **20** (0.13 g, 0.42 mmol), 2'-chloroacetanilide (0.10 g, 0.57 mmol), K_2CO_3 (0.29 g, 2.09 mmol) and acetone (10 mL). The resulting mixture was heated to reflux for 18 h, after which time it was allowed to cool to RT and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 65:35 hexane/ethyl acetate as eluant to afford **17** as a white solid (0.16 g, 85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.34 (s, 1H), 8.70 (d, J= 6 Hz, 1H), 7.80 (m, 3H), 7.68 (m, 3H), 7.55 (dd, J= 9, 3 Hz, 1H), 7.35 (m, 4H), 7.14 (t, J= 6 Hz, 1H), 7.07 (d, J= 9 Hz, 1H), 4.75 (s, 2H).



21

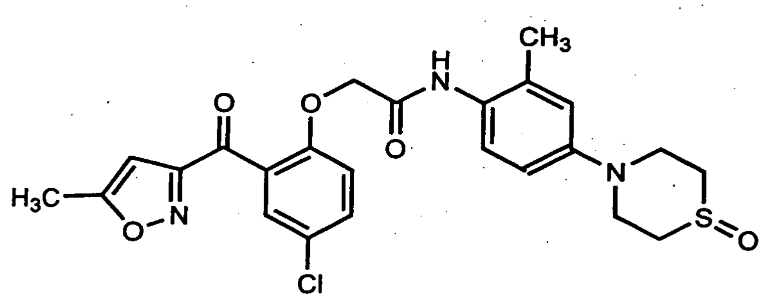
Step A:

it was allowed to cool to rt. The suspension was then filtered through a pad of celite, which was washed with several portions of CH_2Cl_2. The solvents were removed under reduced pressure to afford a tan solid (6.55 g, 95%). The solid was used in subsequent reactions without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.94 (d, J= 3 Hz, 1H), 8.81 (dd, J= 6, 3 Hz, 1H), 8.19 (m, 1H), 7.49 (m, 2H), 6.98 (d, J= 9 Hz, 1H), 3.74 (s, 3H).

Step C:

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **23** (6.55 g, 26.45 mmol) and CH_2Cl_2 (200 mL). The resulting solution was cooled to –78 °C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol) was added via syringe. The resulting solution was allowed to stir at –78 °C for 1 h, after which time it was allowed to warm to rt and stir for an additional 30 min. The mixture was carefully poured over ice water and the resulting two-phase system was stirred for 30 min. It was then poured into a separatory funnel containing water and CH_2Cl_2. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **21** as a yellow solid (5.25 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.77 (s, 1H), = 3 Hz, 1H), 8.90 (dd, J = 3, 1.5 Hz, 1H), 8.07 (m, 1H), 7.55 (m, 3H), 7.11 (m, 1H).

Example 9:



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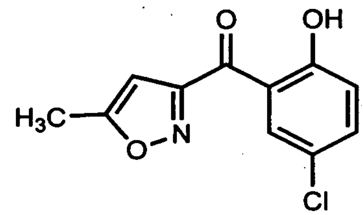
$MgSO_4$, filtered and the solvents were removed under reduced pressure to provide a white solid (5.37 g, 94%). [1]H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, J= 3 Hz, 1H), 7.42 (dd J= 6, 3 Hz, 1H), 6.92 (d, J = 6 Hz, 1H), 6.45 (s, 1H), 3.76 (s, 3H), 2.49 (s, 3H).

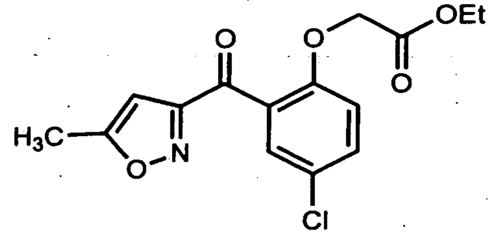
Step C:



27

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **26** (5.36 g, 21.30 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and boron tribromide (40 mL of a 1.0 M solution in CH_2Cl_2) was added via syringe. The resulting dark red solution was allowed to stir at –78 °C for 1 h, after which time it was allowed to warm to RT and stir for an additional 2 h. The mixture was then carefully poured over ice water and the resulting two-phase system was stirred for 30 min. The mixture was then poured into a separatory funnel containing Et_2O and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a tan solid (5.44 g) which was used in subsequent reactions without any further purification.

Step D:



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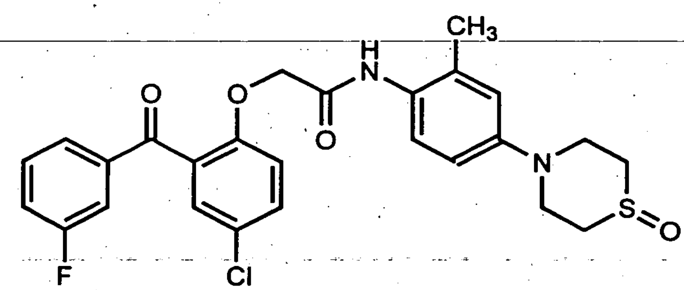
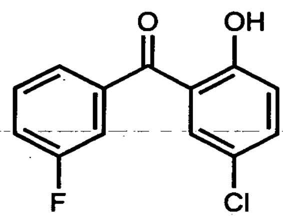


30

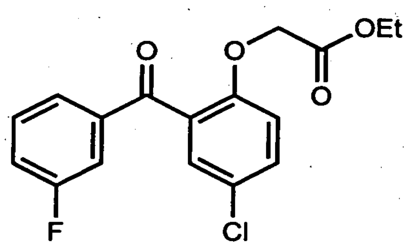


Step A:

31

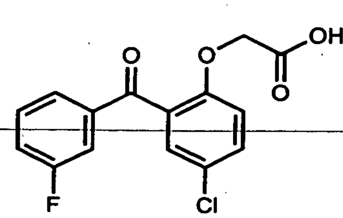
4-Chloroanisole (4.06 g, 28.47 mmol), 3-fluorobenzoyl chloride (4.53 g, 28.57 mmol), $AlCl_3$ (6.23 g, 46.72 mmol) and CH_2Cl_2 (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide the **31** as a yellow solid (2.60 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.80 (s, 1H), 7.50 (m, 6H), 7.09 (d, J= 9 Hz, 1H).

Step B:



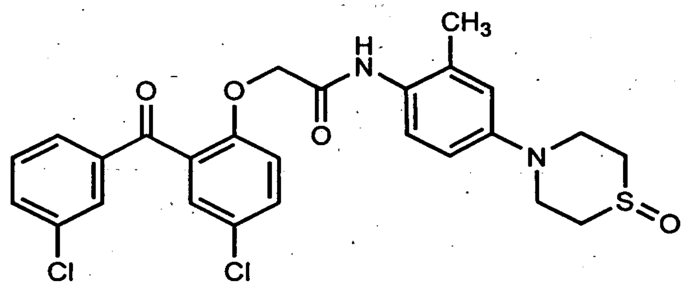
32

Phenol **31** (2.60 g, 10.37 mmol), ethyl bromoacetate (1.3 mL, 11.72 mmol), K_2CO_3 (7.15 g, 51.73 mmol), and acetone (80 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.



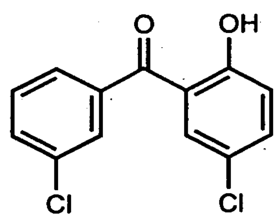
dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **34** as a white solid (0.117 g, 34%). ^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 7.71-7.52 (m, 9H), 7.31-7.27 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

Example 12:



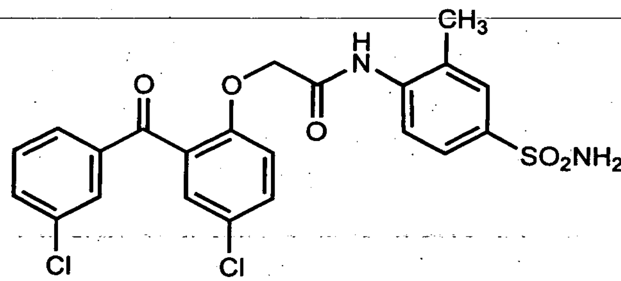
35

Step A:



36

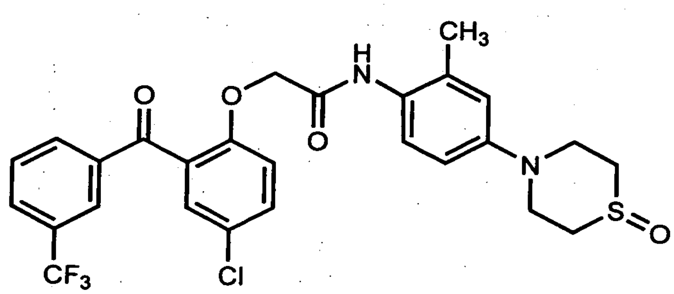
4-Chloroanisole (4.02 g, 28.19 mmol), 3-chlorobenzoyl chloride (3.8 mL, 4.94 g, 28.22 mmol), $AlCl_3$ (5.62 g, 42.15 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide **36** as a yellow solid (5.35 g, 71%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 1H), 7.64 (s, 1H), 7.58 (d, J= 8 Hz, 1H), 7.53-7.44 (m, 4H), 7.03 (d, J= 12 Hz, 1H).



39

Carboxylic acid **38** (0.229 g, 0.704 mmol), oxalyl chloride (0.2 mL, 2.29 mmol) and CH_2Cl_2 (4 mL) were used according to general procedure V. Into a separate flask were placed sulfonamide **466** (0.156 g, 0.838 mmol), Et_3N (0.25 mL, 1.79 mmol) and CH_3CN (8 mL). The acid chloride (in 2 mL of CH_3CN) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 5 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **39** as a white solid (0.110 g, 32%). ^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 7.82-7.53 (m, 9H), 7.30 (m, 3H), 4.84 (s, 2H), 2.20 (s, 3H).

Example 14:

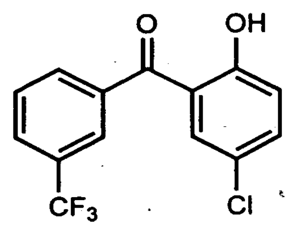


40

Step A:

dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave a yellow oil, which was used in subsequent reactions without any further purification.

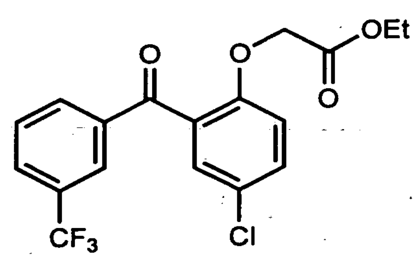
Step C:



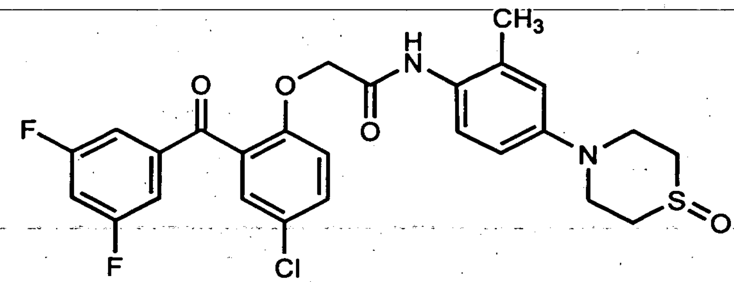
43

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **42** (23 mmol) and CH_2Cl_2 (150 mL). The solution was cooled to –78 °C and boron tribromide (35 mL of a 1.0 M solution in CH_2Cl_2, 35 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a yellow solid (5.04 g, 73%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.76 (s, 1H), 8.25-7.84 (m, 3H), 7.73 (t, J= 9 Hz, 1H), 7.56-7.52 (m, 2H), 7.12 (d, J= 9 Hz, 1H).

Step D:

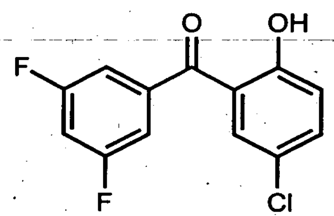


44



46

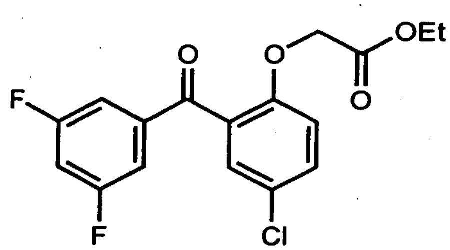
Step A:

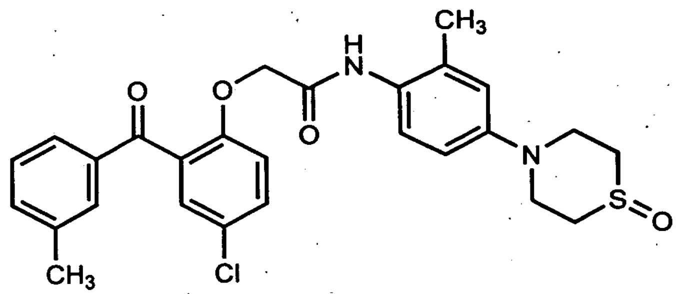


47

4-Chloroanisole (4.12 g, 28.89 mmol), 3,5-difluorobenzoyl chloride (5.0 g, 28.3 mmol), $AlCl_3$ (5.65 g, 42.37 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide a yellow solid (2.72 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.64 (s, 1H), 7.54 (m, 2H), 7.23 (m, 2H), 7.11 (m, 2H).

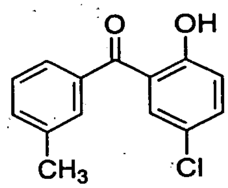
Step B:



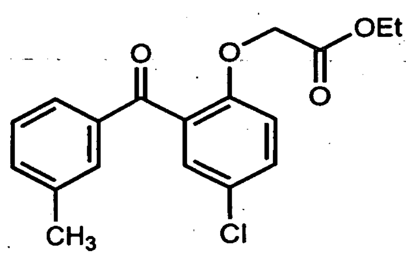


50

Step A:



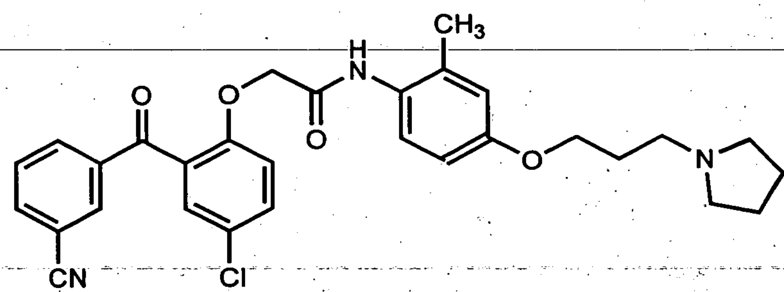
4-Chloroanisole (4.16 g, 29. 17 mmol), 3-methylbenzoyl chloride (4.42 g, 28.59 mmol), $AlCl_3$ (6.12 g, 45.9 mmol) and CH_2Cl_2 (150 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide **50** as yellow solid (1.54 g, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.91 (s, 1H), 7.54 (d, J= 4 Hz, 1H), 7.47-7.39 (m, 5H), 7.02 (d, J= 8 Hz, 1H), 2.44 (s, 3H).



Step B:

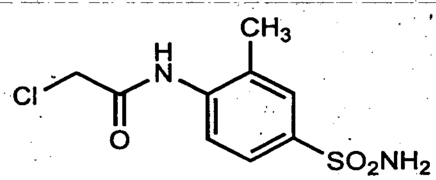
51

Phenol **50** (1.54 g, 6.24 mmol), ethyl bromoacetate (0.8 mL, 7.21 mmol), K_2CO_3 (3.15 g, 22.79 mmol) and acetone (35 mL) were used according to general procedure II. Removal



53

Carboxylic acid **129** (0.316 g, 1.00 mmol), amine **143** (0.241 g, 1.03 mmol), EDAC (0.251 g, 1.31 mmol), HOBt (0.167 g, 1.24 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified



54

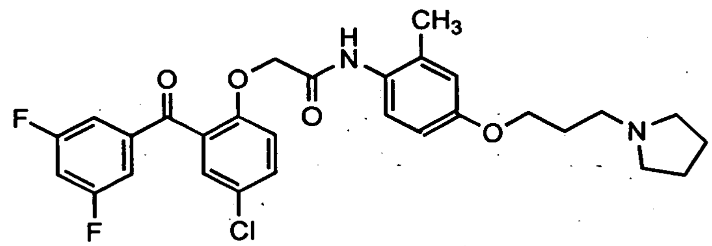
by flash chromatography using 9:1 $CHCl_3/CH_3OH$ as eluant to provide **53** as a tan powder (0.082 g, 15%).

Into a round-bottom flask were placed aniline **466** (0.246 g, 1.32 mmol), Et_3N (0.9 mL, 0.65 g, 6.5 mmol), $CHCl_3$ (5 mL) and CH_3CN (5 mL). The resulting mixture was cooled to 0 °C and 2-chloroacetyl chloride (0.2 mL, 2.51 mmol) was added dropwise over several minutes. The mixture was allowed to stir at 0 °C for 30 minutes and was then allowed to warm to rt and stir for an additional 30 minutes. The mixture was then poured into a separatory funnel containing H_2O and ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a dark, green oil. Several portions of hexane were added and subsequently removed under reduced pressure to afford **54** as a green solid, which was used without any further purification. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.84 (s, D 1H), 7.69 (m, 3H), 7.31 (s, 2H), 4.38 (s, 2H), 2.31 (s, 3H).

Example 18

δ 9.39 (s, 1H), 8.33 (d, J= 3 Hz, 1H), 8.16 (d, J= 3 Hz, 1H), 7.83-7.64 (m, 5H), 7.39-7.30 (m, 3H), 4.86 (s, 2H), 2.23 (s, 3H).

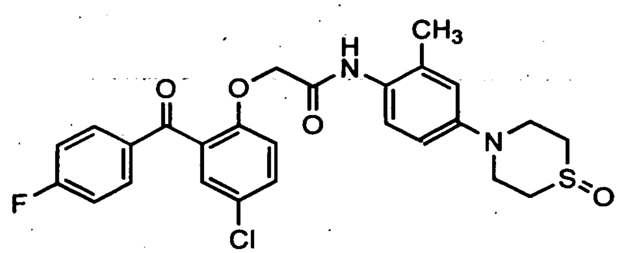
Example 20



57

Acid **49** (0.351 g, 1.07 mmol), amine **143** (0.253 g, 1.08 mmol), EDAC (0.341 g, 1.78 mmol), HOBt (0.193 g, 1.43 mmol) and DMF (7 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 9:1 $CHCl_3/CH_3OH$ to provide a tan solid (0.09 g, 15%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 1H), 7.49 (dd, J= 9, 3 Hz, 1H), 7.42 (d, J= 9 Hz, 1H), 7.33 (d, J = 3 Hz, H), 7.27 (d, J= 3 Hz, 1H), 7.19 (m, 1H), 7.01-6.96 (m, 2H), 6.65-6.63 (m, 2H), 4.62 (s, 2H), 4.00-3.96 (t, J= 6 Hz, 2H), 3.76 (m, 2H), 3.23-3.15 (m, 2h), 2.75 (m, 2H), 2.39-2.12 (m, 6H), 2.09 (s, 3H).

Example 21



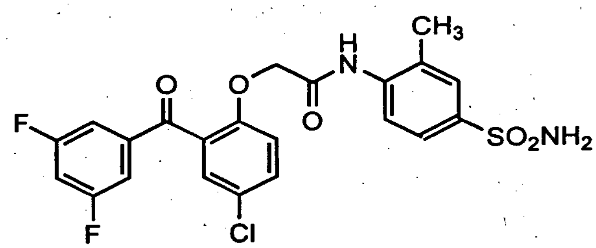
58

filtered and dried to provide 61 as a white solid, which was used without any further purification.

Step D:

Carboxylic acid **61** (0.237 g, 0.786 mmol), sulfoxide 399 (0.198 g, 0.88 mmol), EDAC (0.285 g, 1.49 mmol), HOBt (0.131 g, 0.97 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **58** as a tan solid (0.280 g, 71%). ^{1}H NMR (DMSO-d-$_6$, 300 MHz) δ 8.95 (s, 1H), 7.90 (m, 2H), 7.66 (dd, J= 9, 3 Hz, 1H), 7.49 (d, j= 3 Hz, 1H), 7.36 (t, J= 6 Hz, 2H), 7.26 (d, J= 9 Hz, 1H), 7.14 (d, J= 9 Hz, 1H), 6.84 (m, 2H), 4.73 (s, 2H), 3.75 (m, 2H), 3.58 (m, 2H), 2.91 (m, 2H), 2.71 (m, 2H), 2.03 (s, 3H).

Example 22



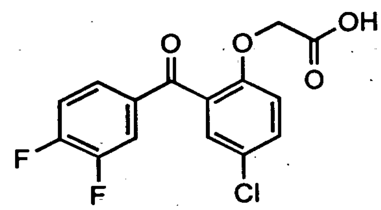
62

Carboxylic acid **49** (0.123 g, 0.377 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (2 drops) and chloroform (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, sulfonamide **466** (0.07 g, 0.37 mmol), $NaHCO_3$ (0.13 g, 1.55 mmol), water (1 mL) and acetone (5 mL) were used according to general procedure VI to afford 62 as a tan solid (0.07 g, 40%). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 9.46 (s, 1H), 7.68-7.45 (m, 8H), 7.28 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

Example 23

Phenol **64** (2.65 g, 9.86 mmol), ethyl bromoacetate (1.20 mL, 10.82 mmol), K_2CO_3 (5.37 g, 38.85 mmol) and acetone (35 mL) were used according to general procedure II to provide 65 as white solid (3.39 g, 96%) that was used without any further purification.

Step C:



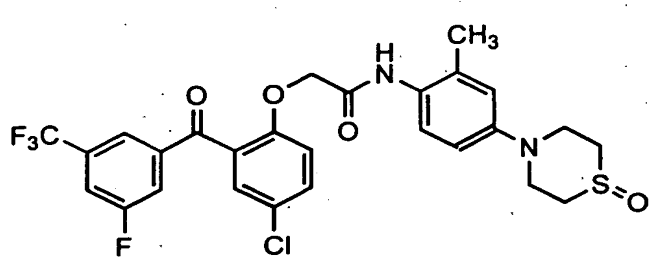
66

Ester **65** (3.39 g, 9.56 mmol), lithium hydroxide (0.80 g, 19.07 mmol), water (20 mL), THF (40 mL) and EtOH (20 mL) were used according to general procedure III to provide **66** as a white solid which was used without any further purification.

Step D:

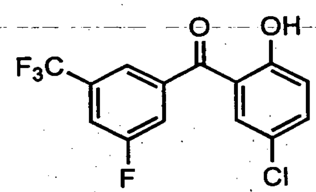
Carboxylic acid **66** (0.146 g, 0.447 mmol), sulfoxide **399** (0.096 g, 0.429 mmol), EDAC (0.183 g, 0.955 mmol), HOBt (0.077 g, 0.569 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **63** as a tan solid (0.150 g, 63%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H), 7.79-7.56 (m, 3H), 7.41 (d, J= 3 Hz, 1H), 7.32 (m, 2H), 7.09 (d, J= 9 Hz, 1H), 6.87 (br s, 1H), 4.73 (s, 2H), 4.04 (m, 2H), 3.58 (m, 2H), 3.02 (m, 4H), 1.62 (s, 3H).

<u>**Example 24**</u>



which time amide **68** (5.04 g, 20.07 mmol) was added dropwise. The mixture was allowed to stir at – 78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 2 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure afford 69 as a yellow solid (6.14 g, 92%), which was used in subsequent reactions without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.68 (d, J= 9 Hz, 1H), 7.58-7.51 (m, 2H), 7.44 (d, J= 3 Hz, 1H), 7.00 (d, J= 9 Hz, 1H), 3.74 (s, 3H).

Step C:

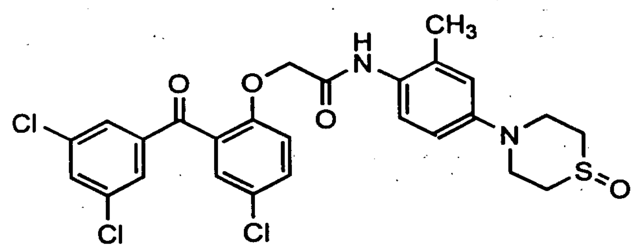


70

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **69** (6.14 g, 18.46 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **70** as a yellow solid (5.68 g, 96%), which was used without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.61 (s, 1H), 7.77 (s, 1H), 7.65-7.54 (m, 3H), 7.47 (d, J= 3 Hz, 1H), 7.12 (d, J= 9 Hz, 1H).

72

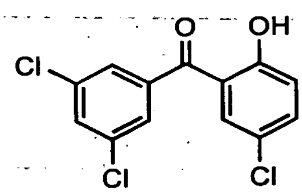
Carboxylic acid **105** (0.195 g, 0.65 mmol), 6-aminobenzthiazole (Lancaster, 0.105 g, 0.70 mmol), EDAC (0.23 g, 1.20 mmol), HOBt (0.105 g, 0.78 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 1:1 hexane/ethyl acetate as eluant to provide **72** as a white solid (0.24 g, 87%). ^1H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H), 8.92 (s, 1H), 8.64 (s, 1H), 8.08 (d, J= 8 Hz, 1H), 7.92 (d, J= 8 Hz, 1H), 7.67-7.63 (m, 2H), 7.55-7.50 (m, 3H), 7.42 (s, 1H), 7.04 (d, J= 8 Hz, 1H), 4.73 (s, 2H).



Example 26

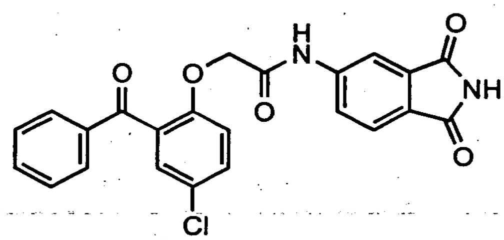
73

Step A:



74

3,5-Dichlorobenzoyl chloride (5.0 g, 23.87 mmol), 4-chloroanisole (3.40 g, 23.84 mmol), aluminum chloride (5.56 g, 41.70 mmol) and dichloromethane (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/dichloromethane to provide **74** as a yellow solid (1.18 g, 16%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.62 (s, 1H), 7.65 (s, 1H), 7.56-7.49 (m, 4H), 7.09 (d, J= 9 Hz, 1H).

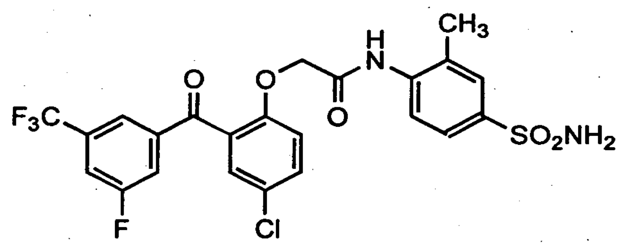


Example 27

77

Carboxylic acid **105** (0.125 g, 0.417 mmol), 3-aminophthalimide (TCI, 0.062 g, 0.382 mmol), EDAC (0.132 g, 0.689 mmol), HOBt (0.063 g, 0.467 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **77** as a white solid (0.038 g, 22%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.10 (s, 1H), 8.39 (s, 1H), 8.25 (dd, J= 9, 3 Hz, 1H), 7.97 (d, J= 9 Hz, 2H), 7.80 (d, J= 9 Hz, 1H), 7.73 (t, J= 6 Hz, 1H), 7.63-7.56 (m, 4H), 7.48 (d, J= 3 Hz, 1H), 7.10 (d, J= 9 Hz, 1H), 4.82 (s, 2H).

Example 28

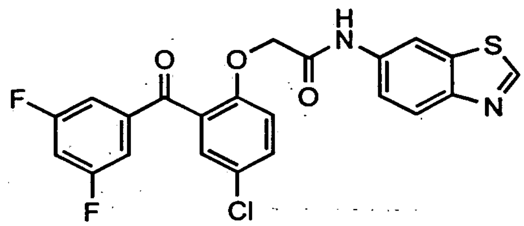


78

Carboxylic acid **71** (11.24 g, 29.84 mmol), oxalyl chloride (3.9 mL, 44.71 mmol), DMF (5 mL) and chloroform (250 mL) were used according to general procedure V to prepare the acid chloride, which was used without further purification. The acid chloride, sulfonamide **466** (5.12 g, 27.49 mmol), $NaHCO_3$ (11.12 g, 132 mmol), acetone (300 mL) and water (10 mL) were used according to general procedure VI. The product was purified by crystallization from a mixture of acetonitrile/water to provide **78** as a white solid (9.01 g, 60%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.47 (s, 1H), 8.05 (d, J= 9 Hz, 1H), 7.93-7.90 (m,

77%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.18 (s, 1H), 9.30 (s, 1H), 8.50 (s, 1H), 8.26 (s, 1H), 8.13 (d, J= 9 Hz, 1H), 8.05 (t, J= 9 Hz, 2H), 7.75-7.66 (m, 2H), 7.56 (m, 2H), 7.26 (d, J= 9 Hz, 1H), 4.81 (s, 2H).

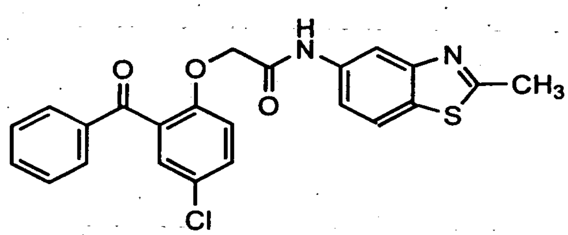
Example 31



81

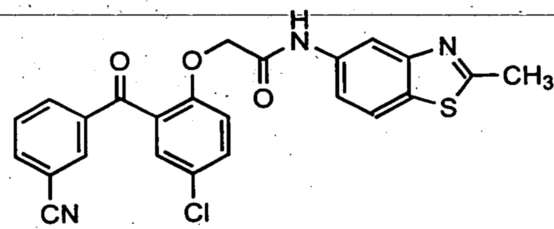
Carboxylic acid **49** (0.106 g, 0.324 mmol), 6-aminobenzthiazole (Lancaster, 0.051 g, 0.3393 mmol), EDAC (0.158 g, 0.824 mmol), HOBt (0.0584 g, 0.429 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **81** as a white solid (0.105 g, 70%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1H), 9.31 (s, 1H), 8.48 (d, J= 3 Hz, 1H), 8.04 (d, J= 9 Hz, 1H), 7.67 (dd, J= 9, 3 Hz, 1H), 7.59-7.48 (m, 5H), 7.25 (d, J= 9 Hz, 1H), 4.82 (s, 2H).

Example 32



82

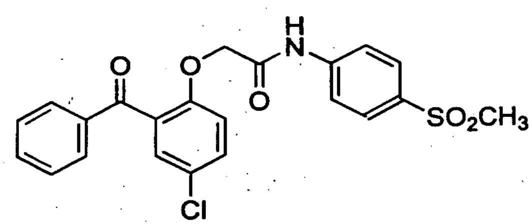
Carboxylic acid **105** (0.129 g, 0.43 mmol), oxalyl chloride (0.1 mL, 1.1 5mmol), DMF (4 drops) and dichloromethane (3 mL) were used to prepare the acid chloride according to



84

Carboxylic acid **129** (0.094 g, 0.298 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.068 g, 0.287 mmol), $NaHCO_3$ (0.310 g, 3.69 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **84** as a tan solid (0.042 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.09 (s, 1H), 8.22 (d, J= 9 Hz, 2H), 8.13 (d, J= 6Hz, 1H), 8.06 (d, J= 9 Hz, 1H), 7.94 (d, J= 9 Hz, 1H), 7.75-7.66 (m, 2H), 7.55 (d, J= 3 Hz, 1H), 7.49 (d, J= 3 Hz, 1H), 7.25 (d, J= 6 Hz, 1H), 4.78 (s, 2H), 2.80 (s, 3H).

Example 35



85

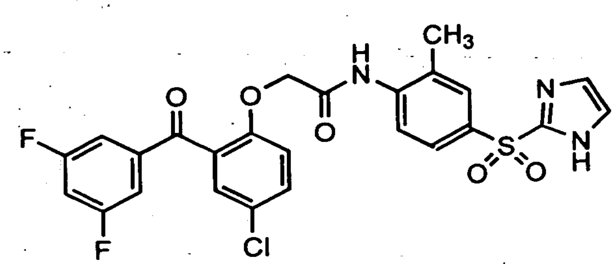
Carboxylic acid **105** (0.104 g, 0.347 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (4 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, 4-methylsulfonlylaniline (0.06 g, 0.350 mmol), $NaHCO_3$ (0.214 g, 2.55 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI. The product was purified by flash chromatography using 3:2

Compound **87** (1.26 g, 6.97 mmol), iron powder (1.89 g, 33.84 mmol), concentrated hydrochloric acid (7 mL) and ethanol (35 mL) were added to a round-bottom flask. The mixture was heated to reflux and stirred for 2 h, after which time it was allowed to cool to rt. The mixture was then poured into water and was made basic by the slow addition of solid $NaHCO_3$. It was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **88** as a tan solid (0.470 g, 45%). %). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (s, 1H), 7.81 (d, J= 9 Hz, 1H), 7.20 (d, J= 3 Hz, 1H), 6.99 (dd, J= 9, 3Hz, 1H), 5.40 (s, 2H).

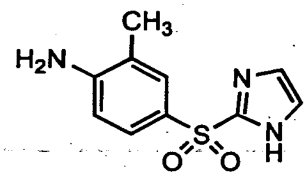
Step C:

Carboxylic acid **129** (0.125 g, 0.396 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, amine **88** (0.063 g, 0.419 mmol), $NaHCO_3$ (0.173 g, 2.06 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI to afford a yellow solid. The solid was washed with several portions of ether and was dried in vacuo to provide **86** as a yellow solid (0.083 g, 47%).

Example 37



89



Step C:

92

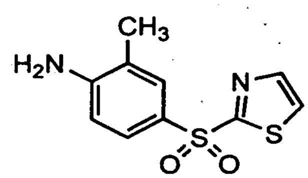
Into a Parr bottle were placed compound **91** (0.092 g, 0.34 mmol), Pd/C (0.01 g, 10% w/w), and ethanol. The bottle was purged with hydrogen (3X) and was finally pressurized to 40 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford **92** as a yellowish solid (0.083 g, >100% yield), which was used without any further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.54 (br s, 1H), 8.77 (s, 1H), 8.74 (s, 1H), 7.60 (dd, J= 8, 4 Hz, 1H), 7.45 (d, J= 4 Hz, 1H), 7.18 (br s, 2H), 7.09 (d, J= 8 Hz, 1H), 2.05 (s, 3H).

Step D:

Carboxylic acid **49** (0.100 g, 0.31 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine **92** (0.065 g, 0.273 mmol), $NaHCO_3$ (0.134 g, 1.59 mmol), water (0.5 mL) and acetone (4 mL) were used according to general procedure VI to afford a tan solid. The solid was washed with several portions of ether and dried to afford **89** as a tan solid (0.105 g, 62%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.74 (s, 1H), 10.26 (s, 1H), 7.70-7.27 (m, 10H), 6.95 (d, J= 9 Hz, 1H), 5.19 (s, 2H), 2.20 (s, 3H).

Into a round-bottom flask were placed compound **94** (0.103 g, 0.41 mmol), glacial acetic acid (3 mL) and hydrogen peroxide (0.210 g of a 30% w/w solution, 1.85 mmol). The resulting mixture was heated to 85-90 °C for 2 h, after which time it was allowed to cool to rt and was poured into a flask containing a saturated solution of sodium bisulfite. The pH of the mixture was adjusted to pH 7 by the slow addition of solid $NaHCO_3$ and was then poured into a separatory funnel containing ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **95** as a white solid (0.103 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10-8.00 (m, 4H), 7.73 (d, J= 4 Hz, 1H), 2.64 (s, 3H).

Step C:



96

Into a Parr bottle were placed compound **95** (0.074 g, 0.34 mmol), Pd/C (0.018 g, 10% w/w), and ethanol (2 mL). The bottle was purged with hydrogen (3X) and was finally pressurized to 45 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford **96** as a yellow oil, which was used without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J= 3 Hz, 1H), 7.87 (d, J= 9 Hz, 1H), 7.74 (s, 1H), 7.65 (d, J= 3 Hz, 1H), 7.31 (d, J= 9 Hz, 1H), 5.81 (br s, 2H), 2.13 (s, 3H).

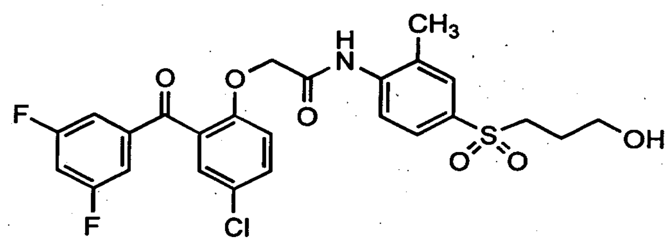
Step D:

Carboxylic acid **49** (0.104 g, 0.31 mmol), oxalyl chloride (0.6 mL of a 2.0 M solution in dichloromethane, 1.2 mmol), DMF (4 drops) and chloroform (4 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine **96**

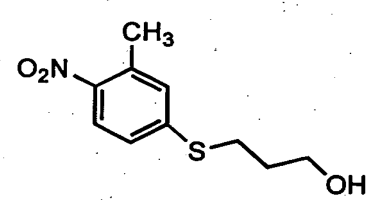
98

Carboxylic acid **49** (0.112 g, 0.343 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, the aniline (prepared according to the method of Brown, E.V., *Journal of Organic Chemistry*, 42(19), 3208-3209, 1977), 0.050 g, 0.312 mmol), $NaHCO_3$ (0.137 g, 1.63 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI to provide **98** as a yellow solid (0.064 g, 44%). ^1H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1H), 8.20 (s, 1H), 7.95 (d, J= 9 Hz, 1H), 7.72 (d, J= 9 Hz, 1H), 7.69-7.47 (m, 7H), 7.37 (s, 1H), 7.23 (d, J= 9 Hz, 1H), 4.81 (s, 2H).

Example 41



99



Step A:

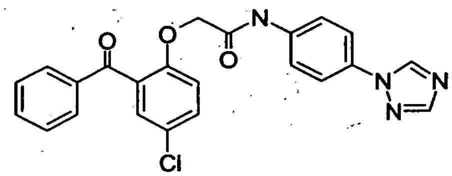
100

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (5.0 g, 32.2 mmol), K_2CO_3 (15.34 g, 111 mmol), 3-mercaptoethanol (3.2 mL, 37 mmol) and DMF (30 mL). The resulting mixture was allowed to stir at rt for 16 h, after which time it was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **100** as thick, yellow oil, which was used without any further purification.

Step D:

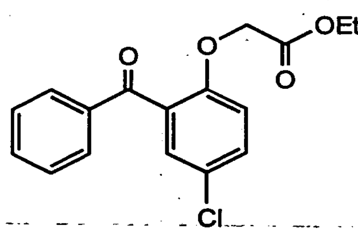
Carboxylic acid **49** (0.302 g, 0.924 mmol), oxalyl chloride (0.15 mL, 1.72 mmol), DMF (4 drops) and chloroform (10 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, amine **102** (0.190 g, 0.86 mmol), $NaHCO_3$ (0.323 g, 4.16 mmol), water (0.5 mL) and acetone (10 mL) were used according to general procedure X to provide **99** as a tan solid (0.326 g, 70%).

<u>Example 43:</u>



103

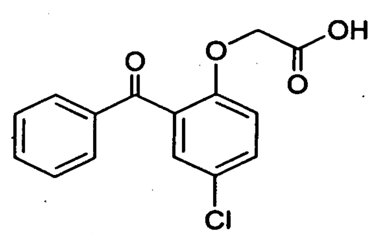
Step A:



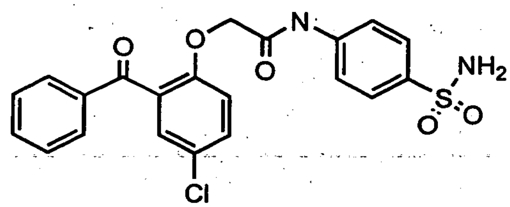
104

This reaction was run according to general procedure II using 5-chloro-2-hydroxybenzophenone (15 g, 64 mmol), ethyl bromoacetate (7.7 mL, 71 mmol) potassium carbonate and (44 g, 320 mmol). A 96% yield of **104** was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.8 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7-7.8 (m, 8H).

Step B:



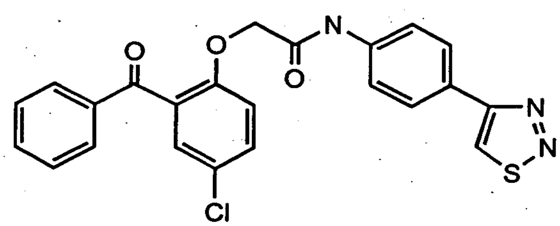
Example 45:



107

Following the procedure described for the synthesis of **103** and using sulfanilamide, a 6% yield of **107** was obtained as a white solid after purification by flash column chromatography on silica gel with 20% acetone in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 6.82 (m, 2H), 7.1-7.8 (m, 12H), 10.1 (s, 1H).

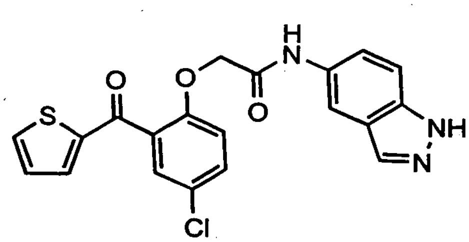
Example 46:



108

Following the procedure described for the synthesis of **103** and using 4-(4-aminophenyl)-1,2,3-thiadizole as the aniline, a 20% yield of **108** was obtained as a gray solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.4-8.1 (m, 112H), 9.41 (s, 1H), 10.0 (s, 1H).

Example 47:



109

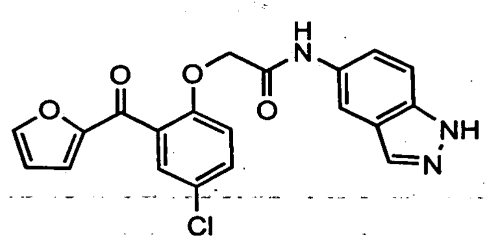
Step A:

Following the procedure described in general procedure III, a 22% yield of **112** was obtained as a solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.05 (d, 1H), 7.18 (t, 1H), 7.41 (d, 1H), 7.42-7.6 (m, 2H), 8.06 (d, 1H).

Step D:

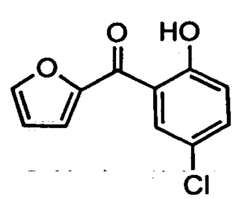
This reaction was run according to general procedure IV using **112** (0.14 g, 0.43 mmol), HOBT (0.06 g, 0.43 mmol), 5-aminoindazole(0.06 g, 0.43 mmol), EDAC (0.08 g, 0.43 mmol) and triethylamine (0.12 mL, 0.86 mmol). A 23% yield of **109** was obtained after purification by flash column chromatography on silica gel with 5% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8 (s, 2H), 7.1-7.3 (m, 2H), 7.32 (d, 1H), 7.46 (d, 1H), 7.48 (s, 1H), 7.56 (d, 1H), 7.7 (d, 1H), 7.98 (s, 1H), 8.04 (s, 1H), 8.1 (d, 1H), 9.8 (s, 1H), 13 (s, 1H).

<u>Example 48:</u>



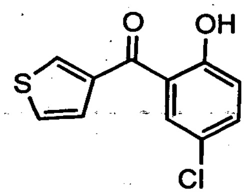
113

Step A:



114

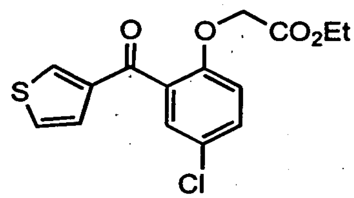
Step A:



117

A mixture of 3-thiophenecarboxyl chloride (3.58 g, 28 mmol) and thionyl chloride (15 mL) was refluxed for 3 h. The reaction mixture was concentrated and further dried in vacuo. The resultant concentrate was added to a suspension of aluminum chloride (7.61g, 56 mmol) and p-chloroanisole (3.41 mL, 28 mmol). The suspension was heated to reflux for 24 h. Water was slowly added to the reaction mixture and this aqueous mixture was extracted with first methylene chloride, then ethyl acetate. The organic solutions were combined and dried over $MgSO_4$. After solvent removal, the crude product was purified by flash column chromatography on silica gel with methylene chloride/hexane (1:1). This gave 0.13 g (2%) of **117** as oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7 (d, 1H), 7.3-7.5 (m, 3H), 7.6-7.7 (m, 1H), 8.2 (m, 1H), 10.4 (s, 1H).

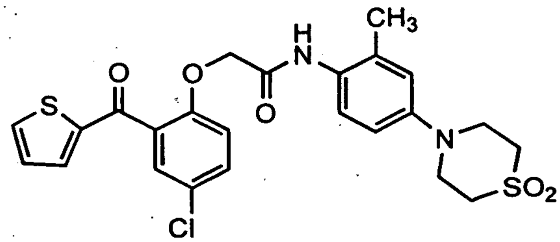
Step B:



118

Following general procedure II, a 45% yield of **118** was obtained as oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.1 (t, 3H), 4.08 (q, 2H), 4.8 (s, 2H), 7.07 (d, 1H), 7.38 (d, 1H), 7.44 (d, 1H), 7.49 (dd, 1H), 7.6 (dd, 1H), 8.11 (d, 1H).

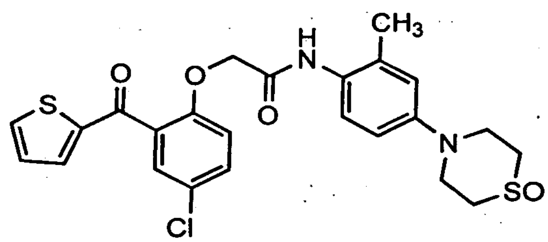
Step C:



121

Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 26% yield of **121** was obtained as a white solid after flash column chromatography on silica gel with 20% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.1 (br s, 4H), 3.7 (s, 4H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

Example 52:



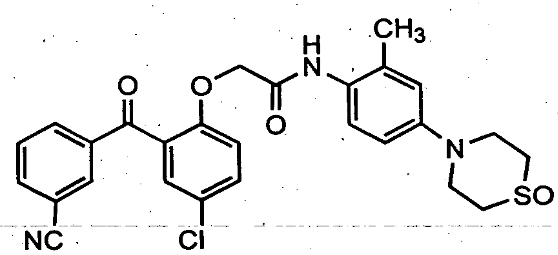
122

Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 24% yield of **122** was obtained as a white solid after flash column chromatography on silica gel with 5% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.6-2.8 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

Example 53:

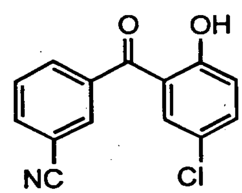
Following the procedure described for the synthesis of compound **103**, a 42% yield **125** was obtained as a white solid after flash column chromatography on silica gel with 3% methanol in methylene chloride. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.2 (s, 3H), 4.8 (s, 2H), 7.1-7.3 (m, 3H), 7.5 (d, 1H), 7.5-7.7 (m, 5H), 7.73 (d, 1H), 8.1 (d, 1H), 9.3 (s, 1H).

Example 56:



126

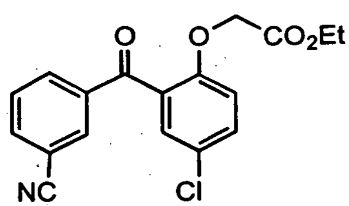
Step A:



127

Following general procedure I, a 9% yield of **127** was obtained after flash column chromatography on gel with 30% hexane in methylene chloride. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 6.97 (d, 1H), 7.38 (s, 1H), 7.42 (d, 1H), 7.7 (t, 1H), 7.98 (d, 1H), 8-8.1 (m, 2H), 10.4 (s, 1H).

Step B:

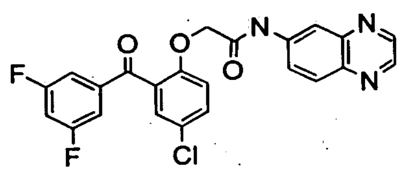


128

Following general procedure II, a quantitative yield of **128** was obtained as oil that was used in the following reaction without any additional purification.

MS (ES(+)): m+1/z 443. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 9.66 (s, 1H), 8.32 (s, 1H), 7.79 (m, 2H), 7.57 (dd, 1H), 7.4 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

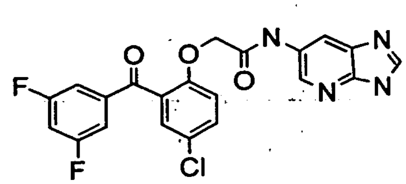
Example 58:



131

Acid **49** (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 ml, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-aminoquinoxaline (0.045 g, 0.3 mmol; prepared by the method of Case, F. H. and Brennan, J. A., JACS, 1959, 81, 6297) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (95:5, v/v) in 15% yield. MS (ES(+)): m+1/z 454. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.64 (s, 1H), 8.18 (dd, 1H), 8.09 (d, 1H), 7.56 (dd, 1H), 7.6 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

Example 59:

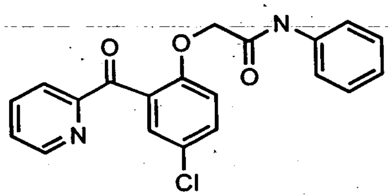


132

Acid **49** (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 mL, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-amino-1H-imidazo[4,5-b]pyridine (0.04 g, 0.3 mmol; which can be prepared by the method of Brooks, W. and Day, A. R., J. Heterocyclic Chem., 1969, 6(5), 759) and sodium bicarbonate (0.2 g, 2.2

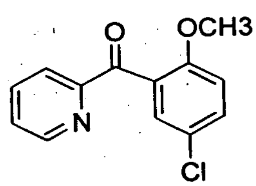
Compound **133** (50 mg, 133 mmol) and Raney-Nickel catalyst (Aldrich, 45 mg, 90% by weight) were added to ethanol (30 mL) and placed on a Parr hydrogenator at 50 psig hydrogen pressure. Additional catalyst (100 mg) was added at 1 h intervals. After 3 h, the catalyst was filtered and the solvents removed in vacuo. The product was purified by chromatography on silica gel eluted with chloroform/methanol (98:2) to obtain 38.6 mg (112 mmol, 84% yield). MS (ES(+)): m+1/z 347. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.06 (s, 1H), 7.90 (d, 2H), 7.60 (m, 3H), 7.48 (m, 2H), 7.30 (t, 2H), 7.09 (t, 1H), 6.90 (d, 1H), 6.84 (dd, 1H), 6.74 (d, 1H), 4.59 (s, 2H), 3.62 (br s, 2H).

Example 62:



135

StepA:

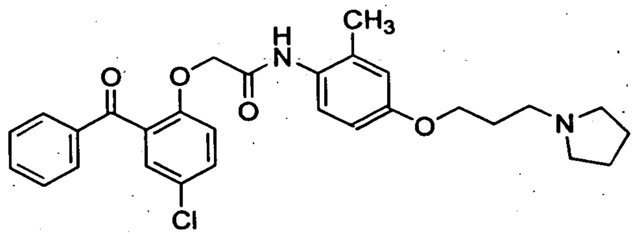


136

2-Bromo-4-chloroanisole (24.4 g, 0.11 mol) was added dropwise to a stirred suspension of magnesium (2.7 g, 0.11 mol) in diethyl ether (150 mL) containing a crystal of iodine. The mixture was heated to reflux for 2 h. A solution of 2-cyanopyridine (11.4 g, 0.11 mol) in diethyl ether (100 mL) was added dropwise and the resulting suspension (yellowish-tan precipitate formed) was refluxed for 2h, cooled to rt and poured into cold 2N HCl (300 mL). The diethyl ether layer was separated and discarded. The aqueous layer was made basic by addition of 50% aq NaOH and extracted with ether (4 x 300 mL). The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to give a brown solid. The product was purified by chromatography on silica gel eluted with ethyl acetate/hexane (1:3) to give 10.9 g, in 40% yield. MS (ES^+) m/z: 248.0 (M+1, 85%), 270

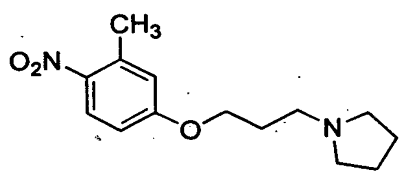
acetonitrile (2 mL) and added to the acid chloride solution. The reaction was stirred at rt for 3 h. A precipitate formed and was filtered. The reaction solvent was removed in vacuo. The product was purified by chromatography on silica gel eluted with hexane/ethyl acetate (3:1, v/v). The product containing fractions were combined and the solvents removed in vacuo to provide a 50% yield. MS (APCI(+)): m+Na/z 404. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 7.85 -7.0(m, 13H), 4.95 (s, 2H).

Example 64:



138

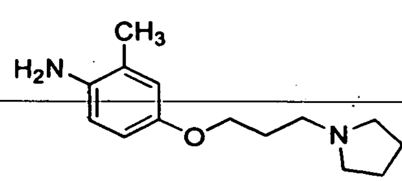
Step A:



139

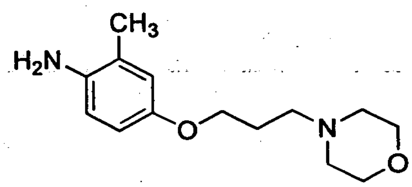
4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene (8.0 g, 29.2 mmol, which can be prepared according to the method found in Patent; Wellcome Foundation; GB 982572; 1960; Chem.Abstr.; EN; 63; 2928b; 1965), pyrrolidine (92.5 mL, 29.2 mmol) and K_2CO_3 (5.0 g, 35 mmol) were mixed together in DMF (30 mL) at rt for 16 h. The reaction mixture was filtered and the solvents were removed under reduced pressure to leave an oil and was dissovled in CH_2Cl_2, washed with aqueous NaOH (1N), water, dried and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford **139** as an orange oil (7.5 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 4H), 2.06 (ddd, 2H), 2.57 (m, 6H), 2.58 (s, 3H), 4.14 (t, 2H), 6.84 (m, 3H), 8.10 (d, 1H).

Step B:



oil (5.1 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (ddd, 2H), 2.38 -2.56 (m, 6H), 2.64 (s, 3H), 3.73 (m, 4H), 4.11 (t, 2H), 6.81 (m, 2H), 8.09 (d, 1H).

Step B:



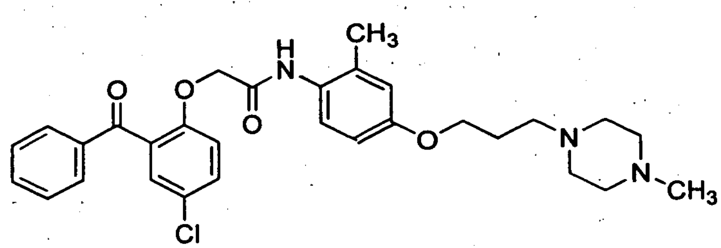
143

Compound **142** (5.1 g, 18.2 mmol) was used in the same manner as that to prepare compound **140**. Amine **143** was obtained as an oil (4.3 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94 (ddd, 2H), 2.19 (s, 3H), 2.49-2.54 (m, 6H), 3.39 (br s, 1H), 3.75 (m, 4H), 3.96 (t, 2H), 6.64-6.70 (m, 3H).

Step C:

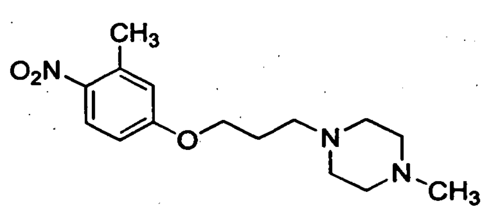
Carboxylic acid **105**, amine **143**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **141** as an oil (1.3 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (ddd, 2H), 2.11 (s, 3H), 2.48-2.56 (m, 6H), 3.75 (m, 4H), 4.02 (t, 2H), 4.68 (s, 2H), 6.6-7.37 (m, 9H), 7.86 (d, 2H), 8.11 (s, 1H).

Example 66:



144

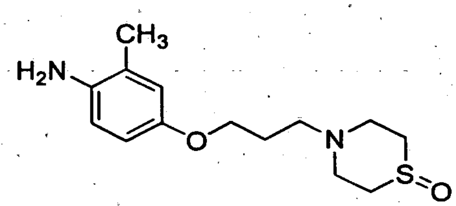
Step A:



147

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and thiomorpholine-1-oxide (5.0 g, 18.2 mmol, which can be prepared according to Nachtergaele, Willy A.; Anteunis, Marc J. O.; Bull.Soc.Chim.Belg.; EN; 89; 7; 1980; 525-536) were used in the same manner as to prepare compound **139**. Compound **147** was obtained as an oil (2.1 g, 37%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (ddd, 2H), 2.65 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m, 8H), 4.12 (t, 2H), 6.82 (m, 2H), 8.10 (s, 1H).

Step B:



148

Compound **147** (2.1 g, 6.7 mmol) was used in the same manner as that to prepare compound **140**. Amine **148** was obtained as an oil (2.1 g, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84 (ddd, 2H), 2.15 (s, 3H), 2.58 (t, 2H), 2.65-3.25 (m, 10H),3.84 (t, 2H), 6.28 (m, 3H).

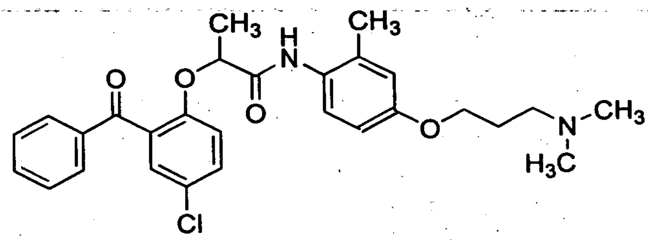
Step C:

Carboxylic acid **105**, amine **148**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **146** as an oil (0.7 g, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (ddd, 2H), 2.71 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m ,8H), 4.00 (t, 2H), 4.67 (s, 2H), 6.72 (s, 2H), 7.03 (d, 2H), 7.38-7.85 (m, 6H), 7.85 (m, 2H), 8.15 (s, 1H).

Example 68:

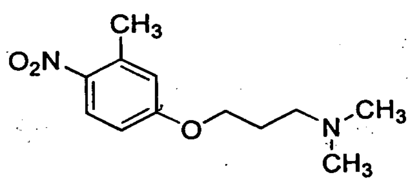
using 95:5 dichloromethane/methanol to afford **149** as an oil (1.1 g, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (ddd, 2 H), 2.18 (s, 3H), 3.80 (t, 2H), 4.18 (t, 2H), 4.63 (s, 2H), 6.60-7.62 (m, 8H), 7.82 (d, 2H), 8.18 (s, 1H).

<u>Example 69:</u>



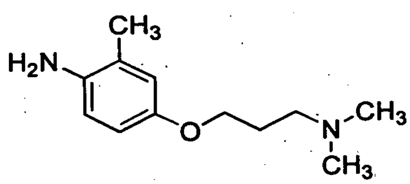
152

Step A:

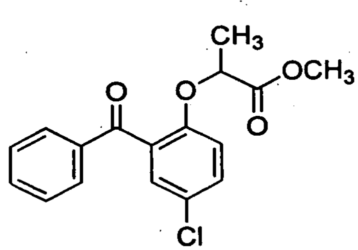


153

Step B:

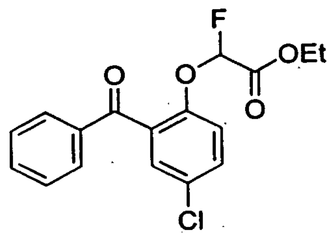


154



Step C:

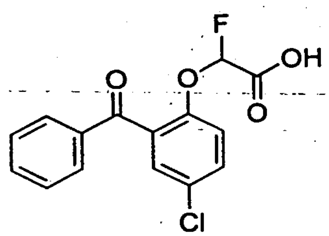
157



Step A:

158

A mixture of 5-chloro-2-hydroxybenzophenone (6.3 g, 27 mmol) ethyl bromofluoroacetate, K_2CO_3 (4.5 g, 32 mmol) and DMF (50 mL) combined and the reaction mixture was allowed to stir at 80 °C for 24 h. The mixture was then filtered, and poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **158** as an oil (7.0 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H), 4.17 (q, 2H), 5.66 (d, 1H), 5.87 (d, 1H), 7.19-8.82 (m, 8H).



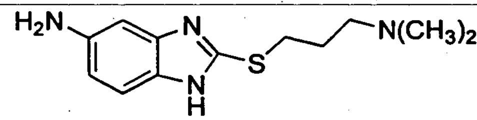
Step B:

159

Ester **158**, water, and ethanol (150 mL) were used according to general procedure III, except that sodium hydroxide (5 mL of a 5N aqueous solution) was used in place of lithium hydroxide. The solvents were removed under reduced pressure to afford **159** as white crystals (5.4 g, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85 (d, 1H), 6.05 (d, 1H), 7.89 (m, 8H).

Step C:

Step B:



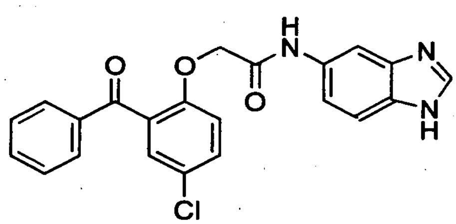
162

Into a stirred Parr bottle were placed compound **161** (1.50 g, 5.36 mmol), Pd/C (0.15 g, 10% w/w), and ethanol (300 mL). The bottle was pressurized to 5 atm. with hydrogen gas and the mixture was allowed to stir at rt for 3 h. The mixture was then filtered through a pad of celite and the solvents were removed under reduced pressure to afford **162** as an orange oil (0.80 g, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (ddd, 2H), 2.27 (s, 6H), 3.18 (t, 2H), 3.47 (br s, 2H), 3.68 (br s, 2H), 6.54 (dd, 1H), 6.71 (s, 1H), 7.26 (dd, 1H), 8.27 (s, 1H).

Step C:

Carboxylic acid **105**, amine **162**, EDAC, HOBt, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford **160** as white crystals (0.24 g, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (ddd, 2H), 2.48 (s, 6H), 2.96 (t, 2H), 3.20 (br s, 2H), 4.62 (s, 2H), 5.22 (s, 1H), 6.86-8.20 (m, 11H), 9.00 (s, 1H).

<u>Example 72:</u>



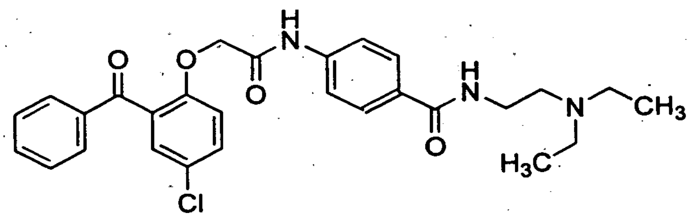
163

Carboxylic acid **105**, 5-aminobenzimidazole, HOBt, EDAC and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **163** as white crystals (0.28 g, 35%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66 (s, 2H), 6.97-8.16 (m, 11H), 9.11 (s, 1H), 10.1 (br s, 1H).

166

Carboxylic acid **105**, 5-aminobenztriazole, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **166** as white crystals (0.75 g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s, 2H), 7.06-8.61 (m, 11H), 9.81 (s, 1H), 12.60 (br s, 1H).

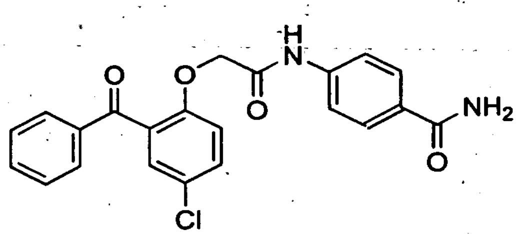
Example 76:



167

Carboxylic acid **105**, N1-[2-(diethylamino)ethyl]-4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **167** as white crystals (0.12 g, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, 6H), 2.83 (q, 4H), 2.90 (dd, 2H), 3.66 (dd, 2H), 4.73 (s, 2H), 7.04-7.95 (m, 13H), 9.43 (s, 1H).

Example 77

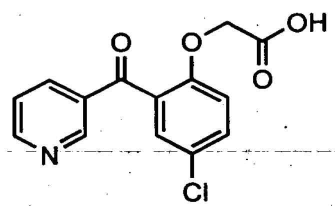


168

Carboxylic acid **105**, 4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **168** as white crystals (0.13 g, 13%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.75 (s, 2H), 5.34 (s, 2H), 7.06-7.97 (m, 12H), 9.53 (s, 1H).

(0.79 mL, 1.18 g, 7.1 mmol) and acetone (150 mL) were used according to general procedure II to provide **171** as an oil (4.0 g, >100%). The product was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J= 1.6 Hz, 1H), 8.75 (d, J= 4 Hz, 1H), 8.18 (d, J= 7.6 Hz, 1H), 7.43 (m, 3H), 6.78 (d, J= 8.8 Hz, 1H), 4.50 (s, 2H), 4.17 (m, 2H), 1.20 (m, 3H).

Step B:



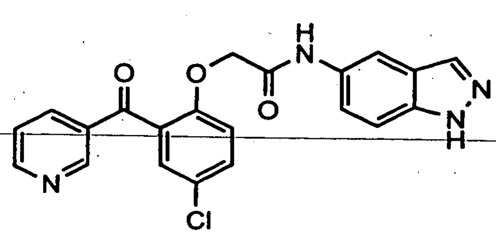
172

Ester **171** (4.0 g, 12.5 mmol), THF (25 mL), water (12 mL), EtOH (12 mL) and LiOH (1.32 g, 31.5 mmol) were used according to general procedure III. Treatment of the resulting yellow gel with ether provided **172** (1.09 g, 29%) as a pale yellow solid. The product was used in the next reaction without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J= 2 Hz, 1H), 8.75 (d, J= 4.8 Hz, 1H), 8.10 (d, J= 8 Hz, 1H), 7.56 (m, 2H), 7.47 (d, J= 2.8 Hz, 1H), 7.10 (d, J= 8.8 Hz, 1H), 4.82 (s, 2H).

Step C:

Carboxylic acid **172** (0.10 g, 0.34 mmol), amine **399** (0.076 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), EDAC (0.19 g, 0.34 mmol), Et_3N (0.1 mL, 0.68 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. Treatment of resulting oil with diethyl ether provided **170** (0.036 g, 21 %) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.88 (s, 1H), 8.75 (s, 1H), 8.10 (d, J= 7.6 Hz, 1H), 7.63 (d, J= 8.8 Hz, 1H), 7.49 (m, 2H), 7.20 (d, J= 8.8 Hz, 1H), 7.05 (d, J= 8.8 Hz, 1H), 6.81 (s, 1H), 6.75 (d, J= 8.8 Hz, 1H), 4.67 (s, 2H), 3.69 (m, 2H), 3.51 (m, 2H), 2.86 (m, 2H), 2.63 (m, 2H), 1.96 (s, 3H).

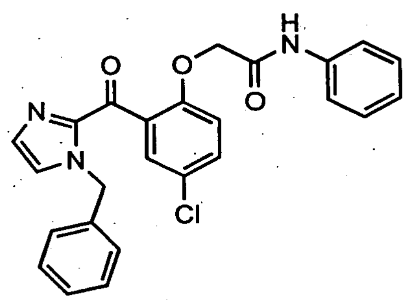
Example 80:



175

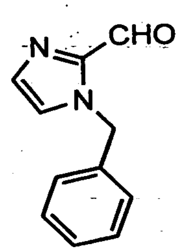
Carboxylic acid **119** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.07 g, 0.51 mmol), EDAC (0.1 g, 0.51 mmol), Et_3N (0.14 mL, 0.10 g, 1.0 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% $MeOH:CH_2Cl_2$ as eluant to provide a yellow oil. Treatment of the oil with diethyl ether provided **175** (0.046 g, 18%) as a pale yellow solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.24 (s, 1H), 7.58 (m, 2H), 7.49 (s, 1H), 7.42 (s, 1H), 7.18 (m, 2H), 6.78 (m, 2H), 4.73 (s, 2H), 3.69 (m, 2H), 3.54 (m, 2H), 2.87 (m, 2H), 2.65 (m, 2H), 2.01 (s, 3H). MS (ES): 503 (M^+).

Example 83:



176

Step A:

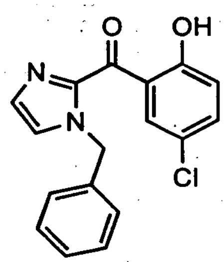


177

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, 1-Benzylimidazole (2.0 g, 12.6 mmol) was dissolved in anhydrous THF (50 mL) and cooled to –78 °C by means of a dry ice/ acetone bath. N-Butyllitium (8.8 mL of a 1.6 M soln. in hexanes, 13.7 mmol) was added dropwise and the reaction was allowed to stir for 15-20 min at –78 °C. Anhydrous N,N-dimethylformamide (1.3 mL, 0.0013 mmol) was added dropwise and reaction was allowed to stir for an additional 45 min at –78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and

pad of celite and the filtrate was concentrated under reduced pressure to provide **179** (1.5 g, >99 %) as a clear gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J= 4 Hz, 1H), 7.37 (m, 4H), 7.32 (m, 3H), 7.11 (s, 1H), 6.91 (d, J= 12 Hz, 1H), 5.71 (s, 2H), 3.75 (s, 3H).

Step D:



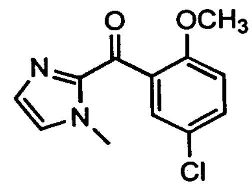
180

Anisole **179** (1.5 g, 4.6 mmol), CH_2Cl_2 (30 mL) and BBr_3 (12 mL of a 1.0 M soln. in CH_2Cl_2, 11.5 mmol) were used according to general procedure IX. The resulting brown oil was filtered through a pad of silica gel using CH_2Cl_2 as eluant and the solvents were removed under reduced pressure to provide **180** (0.9 g, 64%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.34 (m, 9H), 6.96 (d, J= 9 Hz, 1H), 5.65 (s, 2H).

Step E:

In a round bottom flask equipped with a stir bar, reflux condensor and nitrogen on demand were added the phenol **180** (0.1 g, 0.32 mmol), acetone (7 mL), K_2CO_3 (0.22 g, 1.6 mmol) and the amide # (0.058 g, 0.34 mmol). The reaction was allowed to stir at reflux for 18-24 h, after which it was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 3:1 hexanes/ethyl acetate to 1:3 hexanes/ethyl acetate as a solvent gradient to provide **176** (0.077 g, 54 %) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.70 (m, 3H), 7.39 (m, 11H), 6.94 (d, J= 9 Hz, 1H), 5.79 (s, 2H), 4.71 (s, 2H). MS(ES): 445(M^+), 446 $(M+H)^+$.

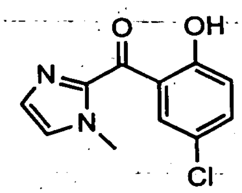
Example 84:



184

In a round bottom flask equipped with a stir bar , an addition funnel and nitrogen on demand, 1-methylimidazole (2.0 g, 24.4 mmol) was dissolved in diethyl ether (50 mL) and cooled to –78 °C by means of a dry ice/ acetone bath. N-Butyllithium (15 mL of a 1.6 M soln. in hexanes, 24.4 mmol) was added dropwise and the reaction was allowed to stir for 30 min at –78 °C. Amide **183** (5.1 g, 22.2 mmol) was added as a solid maintaining reaction temp at –78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 1:1 hexanes/ethyl acetate to provide **184** (3.3 g, 55 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.53 (dd, J= 3, 9 Hz, 1H), 7.42 (d, J= 3 Hz, 1H), 7.17 (m, 1H), 7.13 (s, 1H), 4.03 (s, 3H), 3.73 (s, 3H).

Step D:



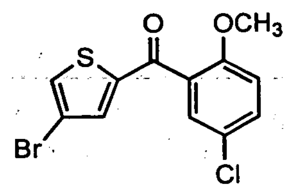
185

Anisole **184** (3.3 g, 13.2 mmol), CH_2Cl_2 (60 mL), and BBr_3 (53 mL of a 1.0 M soln. in CH_2Cl_2, 53 mmol) were used according to general procedure IX to provide **185** (2.0 g, 69%) as a yellow solid. The product was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.83 (d, J= 2 Hz, 1H), 7.62 (s, 1H), 7.56 (dd, J= 3, 9 Hz, 1H), 7.04 (d, J= 9 Hz, 1H), 4.03 (s, 3H).

Step E:

concentrated under reduced pressure to provide **187** (16.3 g, 62%). The product was used in the next step without further purification or characterization.

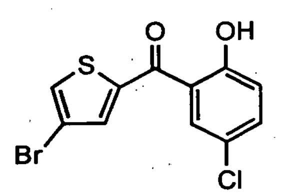
Step B:



188

In a round bottom flask equipped with a stir bar and nitrogen on demand were placed the alcohol **187** (16.3 g, 49 mmol), CH_2Cl_2 (200 mL), and MnO_2 (21.1 g, 240 mmol). The reaction was allowed to stir at RT for 18-24h, after which time the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to provide **188** (2.3 g, 14 %) as an orange oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 7.19 (d, J= 9 Hz, 1H), 3.72 (s, 3H).

Step C:



189

Anisole **188** (2.3 g, 7.0 mmol), CH_2Cl_2 (100 mL), and BBr_3 (21 mL of a 1.0 M soln. in CH_2Cl_2, 21 mmol) were used according to general procedure to provide **189** (2.1 g, 94%) as a yellow solid. The product was used without further purification in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.24 (s, 1H), 7.57 (d, J= 1.2 Hz, 1H), 7.46 (m, 2H), 7.02 (d, J= 9 Hz, 1H).

Step D:

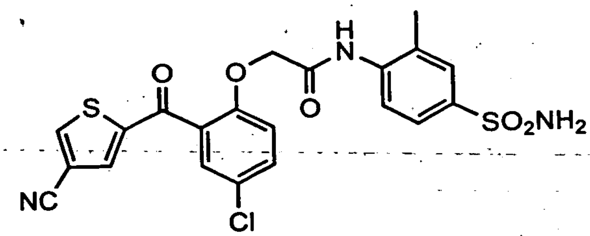
192

Ester **191** (0.7 g, 2 mmol), THF (10 mL), water (5 mL), EtOH (5 mL) and LiOH (0.2 g, 5 mmol) were used according to general procedure III to provide **192** (0.5 g, 80 %) as an orange gel. The product was used in the next step without further purification or characterization.

Step G:

Carboxylic acid **192** (0.16 g, 0.49 mmol), amine **399** (0.13 g, 0.34 mmol), HOBt (0.079 g, 0.34 mmol), EDAC (0.14 g, 0.34 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. Treatment of resulting product with diethyl ether provided **186** (0.052 g, 21 %) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.94 (s, 1H), 8.12 (s, 1H), 7.62 (d, J= 9 Hz, 1H), 7.53 (d, J= 2.4 Hz, 1H), 7.20 (d, J= 9 Hz, 1H), 7.14 (d, J= 9 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J= 8 Hz, 1H), 4.77 (s, 2H), 3.70 (m, 2H), 3.52 (m, 2H), 2.87 (m, 2H), 2.63 (m, 2H), 2.03 (s, 3H). MS(ES): 528 (M^+).

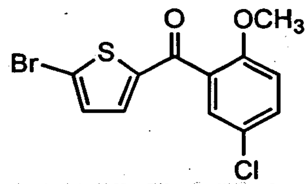
Example 86:



193

In a round bottom flask equipped with a stir bar and nitrogen on demand was added the acid **192** (0.36 g, 1.1 mmol), CH_2Cl_2 (20 mL) and oxalyl chloride (0.1 mL, 0.14 g, 1.1 mmol). The mixture was cooled to 0 °C and N,N-dimethylformamide (1-2 drops) was added. The reaction was allowed to warm to rt over a period of 30-60 min, after which time the mixture was concentrated under reduced pressure to afford the acid chloride. The acid chloride, acetonitrile (20 mL), triethylamine (0.4 mL, 0.29 g, 2.9 mmol) and the sulfonamide (0.26 g, 1.4 mmol) were combined and allowed to stir at RT for 18-24 h. When judged to be complete, the reaction was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and the

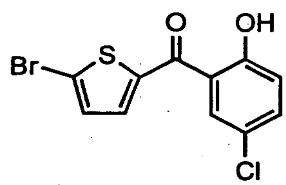
Step B:



196

To a round bottom flask equipped with a stir bar and nitrogen on demand was added the alcohol **195** (20 g, 60 mmol), CH_2Cl_2 (300 mL), and MnO_2 (15.6 g, 180 mmol). The reaction was allowed to stir at RT for 90 min, after which time it was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide **196** (15.3 g, 77 %) as a pale yellow oil. The product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (m, 1H), 7.42 (s, 1H), 7.33 (t, J= 3, 9 Hz, 1H), 7.26 (t, J= 3 Hz, 1H), 7.17 (m, 1H), 3.72 (s, 3H).

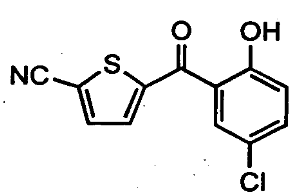
Step C:



197

Anisole **196** (8.2 g, 25 mmol), CH_2Cl_2 (175 mL), and BBr_3 (74 mL of a 1.0 M soln. in CH_2Cl_2, 74 mmol) were used according to general procedure IX to provide **197** (6.8 g, 87%). The product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.39 (dd, J= 2.4, 6 Hz, 1H), 7.35 (m, 4H), 6.94 (dd, J= 3, 9 Hz, 1H).

Step D:



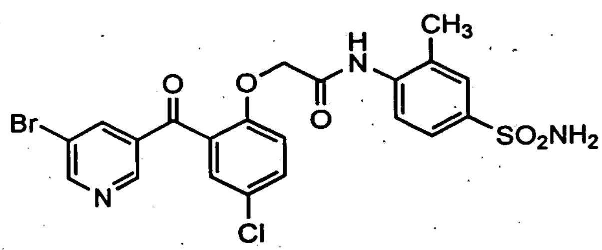
198

as an orange gel. The product was used in the next step without further purification or characterization.

Step G:

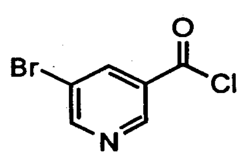
Carboxylic acid **200** (0.42 g, 1.3 mmol), amine **399** (0.36 g, 1.6 mmol), HOBt (0.22 g, 1.6 mmol), EDAC (0.38 g, 2.0 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. The resulting brown oil was purified by flash chromatography using 2 % MeOH/CH_2Cl_2 as eluant. Treatment of the resulting product with diethyl ether provided **194** (0.071 g, 10 %) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.83 (d, J= 4.5 Hz, 1H), 7.69 (m, 2H), 7.61 (s, 1H), 7.27 (d, J= 9 Hz, 1H), 7.18 (d, J= 9 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J= 8.4 Hz, 1H), 4.80 (s, 2H), 3.76 (m, 2H), 3.58 (m, 2H), 2.93 (m, 2H), 2.71 (m, 2H), 2.07 (s, 3 H).

Example 88:



201

Step A:



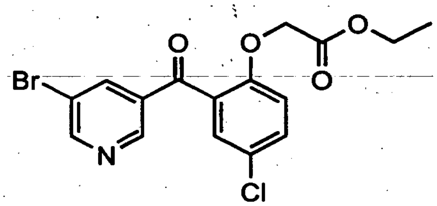
202

5-Bromonicotinic acid (5.0g, 0.025 mol), oxalyl chloride (2.4 mL, 3.5g, 0.027 mol), methylene chloride (125 mL), and N,N-dimethylformamide (2 drops) were used according to general procedure V to provide **202** (6.0g, >100%) as a white solid. The product was

205

Anisole **204** (2.0 g, 6.1 mmol), BBr_3 (18.4 mL of a 1.0 M soln. in CH_2Cl_2, 18.4 mmol), and CH_2Cl_2 (50 mL) were used according to general procedure IX to afford **205** (3.4 g, >100%) as a yellow foam. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.91 (d, J= 2.4 Hz, 1H), 8.75 (d, J= 1.6 Hz, 1H), 8.21 (t, J=2 Hz, 1H), 7.48 (dd, J=2.8, 8.8 Hz, 1H), 7.41 (d, J=2.8 Hz, 1H), 6.97 (d, J=8.8 Hz, 1H). MS (ES): 314 $(M+H)^+$, 312 $(M-H)^-$.

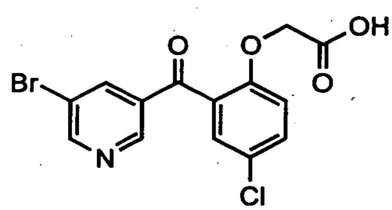
Step E:



206

Phenol **205** (0.55 g, 1.7 mmol), ethyl bromoacetate (0.21 mL, 0.32 g, 1.9 mmol), K_2CO_3 (0.73 g, 5.3 mmol), and acetone (25 mL) were used according to general procedure II to provide **206** (0.58 g, 83%) as a red oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, J= 2.4 Hz, 1H), 8.84 (d, J= 1.8 Hz, 1H), 8.30 (t, J= 1.8 Hz, 1H), 7.66 (dd, J=2.7, 9 Hz, 1H), 7.57 (d, J=2.7 Hz, 1H), 7.19 (d, J= 9 Hz, 1H), 4.82 (s, 2H), 4.18 (m, 2H), 1.2 (m, 3H).

Step F:

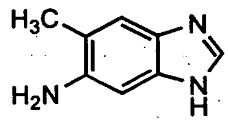


207

Ester **206** (0.58 g, 1.45 mmol), LiOH (0.15 g, 3.64 mmol) and a solution of THF, EtOH, and water (20 mL) were used according to general procedure III. The resulting orange residue was treated with diethyl ether to afford **207** (0.2 g, 42%) as a yellow solid. The product was used the next step without further purification or characterization.

recrystallized using 1:1 methanol:water, making sure to filter any undissolved material while mixture was hot, to obtain **209** (1.8 g, 34 %) as a pale yellow solid. ^1H NMR (300 MHz, DMSO-d_6) δ 12.96 (bs, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.65 (s, 1H), 2.64 (s, 3H). MS (ES): 222 $(M-H)^-$.

Step B:



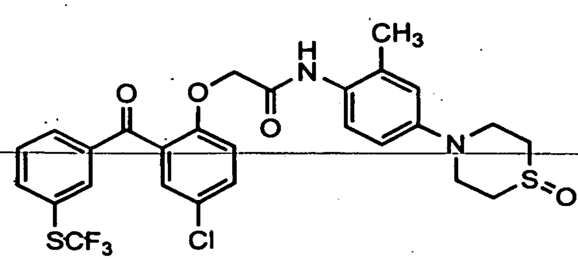
210

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **209** (2.2 g, 0.012 mol), absolute ethanol (75 mL), and palladium on charcoal (0.23 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 psig for 16 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a residue. The residue was washed several times with diethyl ether to afford **210** (1.0g, 57%) as a pink solid. At ambient temperature, the product exists as a mixture of tautomers. ^1H NMR (300 MHz, DMSO-d_6, 100 °C) δ 11.60 (bs, 1H), 7.79 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 4.39 (bs, 2H), 2.20 (s, 3H). MS (ES): 148 $(M+H)^+$.

Step C:

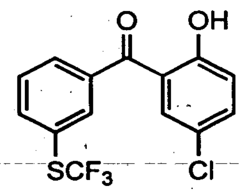
Acid **207** (0.1 g, 0.27 mmol), HOBt (40 mg, 0.27mmol), EDAC (52 mg, 0.27 mmol), , aniline **210** (40 mg, 0.27 mmol), and N,N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH: 1% Et_3N: $CHCl_3$ as eluant to afford **208** (7.6 mg, 5%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.85 (m, 2H), 8.30 (s, 1H), 8.12 (s, 1H), 7.66 (d, J= 7 Hz, 1H), 7.53 (m, 2H), 7.37 (m, 1H), 7.23 (d, J= 9 Hz, 1H), 4.75 (s, 2H), 2.12 (s, 3H). MS (ES): 501 $(M+H)^+$.

<u>Example 90:</u>



Amide **213** (0.8 g, 3.0 mmol), n-butyllithium (1.3 mL of a 2.5 M soln. in hexanes, 3.3 mmol), 2-bromo-4-chloroanisole (0.41 mL, 0.66 g, 3.0 mmol), and diethyl ether (10 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluant to afford **214** (0.56 g, 55%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J= 8 Hz, 1H), 7.87 (m, 2H), 7.68 (d, J= 8 Hz, 1H), 7.60 (dd, J= 2.4, 8.8 Hz, 1H), 7.45 (d, J=2.8 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 3.62 (s, 3H).

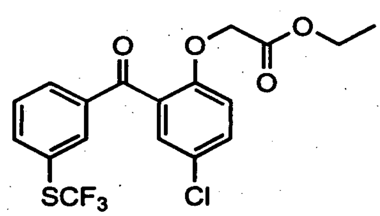
Step D:



215

Anisole **214** (0.56 g, 1.6 mmol), BBr_3 (2.0 mL of a 1.0 M soln. in CH_2Cl_2, 2.0 mmol), and CH_2Cl_2 (10 mL) were used according to general procedure IX to afford **215** (0.45 g, 86%). The product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.95 (m, 2H), 7.87 (d, J= 8 Hz, 1H), 7.66 (t, J=8 Hz, 1H), 7.44 (dd, J=2.8, 8.8 Hz, 1H), 7.35 (d, J=2.8 Hz, 1H), 6.96 (d, J=8.8 Hz, 1H). MS (ES): 331 $(M-H)^-$

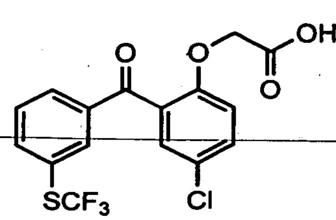
Step E:



216

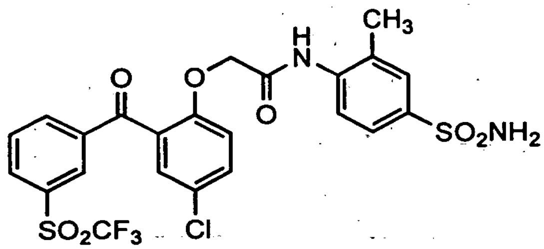
Phenol **215** (0.45 g, 1.4 mmol), ethyl bromoacetate (0.17 mL, 0.25 g, 1.5 mmol), K_2CO_3 (0.48 g, 2.5 mmol), and acetone (20 mL) were used according to general procedure II to provide **216** (0.6 g, >100%) as a yellow oil. The product was used in the next step without further purification or characterization.

Step F:



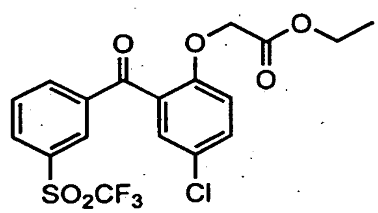
diethyl ether to afford **218** (50 mg, 45%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.38 (m, 3H), 8.01 (m, 1H), 7.70 (m, 5H), 7.31 (m, 3H), 4.80 (s, 2H), 2.16 (s, 3H). MS (ES): 559 (M^+).

Example 92



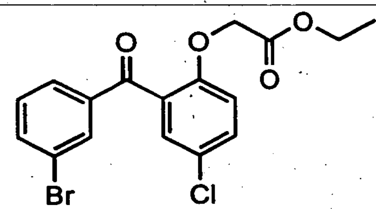
219

Step A:



220

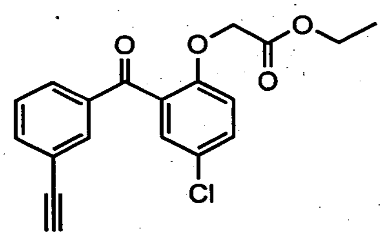
To a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were placed the ester **216** (0.56 g, 1.34 mmol) and CH_2Cl_2 (25 mL) and the reaction mixture was cooled to 0 °C. A solution of m-chloroperoxybenzoic acid in CH_2Cl_2 (10 mL) was added dropwise via addition funnel and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 16 h. When judged to be complete, the reaction was quenched with 10% sodium metabisulfite solution and extracted with CH_2Cl_2. The organics were collected, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford **220** (0.56 g, 93%) as a pale yellow oil. The product was used in the next reaction without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J= 8 Hz, 1H), 8.29 (d, J= 8 Hz, 1H), 8.22 (s, 1H), 7.96 (t, J= 7.6 Hz, 1H), 7.62 (dd, J= 2.8, 9.2 Hz, 1H), 7.55 (d, J=2.8 Hz, 1H), 7.17 (d, J=8.8 Hz, 1H), 4.70 (s, 2H), 4.05 (m, 2H), 1.21 (m, 3H).



223

Phenol **432** (10 g, 0.032 mol), ethyl bromoacetate (3.5 mL, 5.3 g, 0.032 mol), K_2CO_3 (11 g, 0.080 mol), and acetone (120 mL) were used according to general procedure II to afford **223** (11.5 g, 91%) as a yellow oil. The product was used in the next step without further purification. [1]H NMR (400 MHz, DMSO-d$_6$) δ 7.82 (m, 2H), 7.68 (d, J= 7.6 Hz, 1H), 7.53 (dd, J= 2.4, 8.8 Hz, 1H), 7.44 (m, 2H), 7.09 (d, J= 9.2 Hz, 1H), 4.74 (s, 2H), 4.04 (q, J= 7.2 Hz, 2H), 1.13 (m, 3H).

Step B:



224

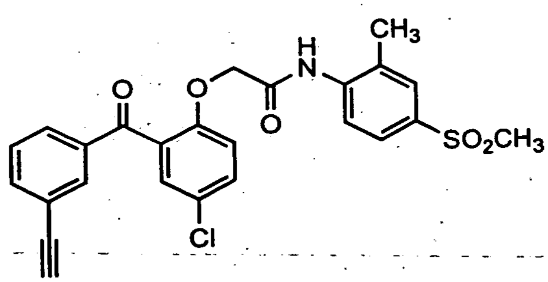
To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (1.5 g, 3.8 mmol), trimethylsilylacetylene (0.6 mL, 0.4 g, 4.1 mmol), tetrakis(triphenylphosphine)palladium (0) (0.31 g, 0.27 mmol), copper(I) iodide (0.15 g, 0.80 mmol), triethylamine (1.7 mL, 1.2 g, 0.80 mmol), and N,N-dimethylformamide (15 mL) and the reaction was allowed to stir at 80 °C for 18h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water and brine, dried over Na_2SO_4, filtered through a pad of celite, and the solvents were removed under reduced pressure. To the resulting residue was added tetrahydrofuran (20 mL) and tetrabutylammonium fluoride (3 mL). The mixture was allowed to stir at RT for 10 min, after which it was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The resulting product

226

Step A:

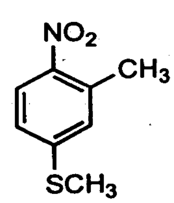
Acid **225** (80 mg, 0.25 mmol), oxalyl chloride (0.024mL, 35mg, 0.28 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (3 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (48 mg, 0.26 mmol), $NaHCO_3$ (105 mg, 1.3 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **226** (20 mg,16%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.77 (d, J= 7.6 Hz, 1H), 7.70 (d, J= 7.6 Hz, 1H), 7.58 (m, 4H), 7.45 (m, 2H), 7.22 (m, 3H), 4.77 (s, 2H), 4.27 (s, 1H), 2.13 (s, 3H). MS ES): 482 (M^+), 481 $(M-H)^-$.

<u>**Example 95**</u>



227

Step A:



228

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added 5-fluoro-2-nitrotoluene (2.4 mL, 3.0 g, 0.019 mol), sodium thiomethoxide (1.5 g, 0.021

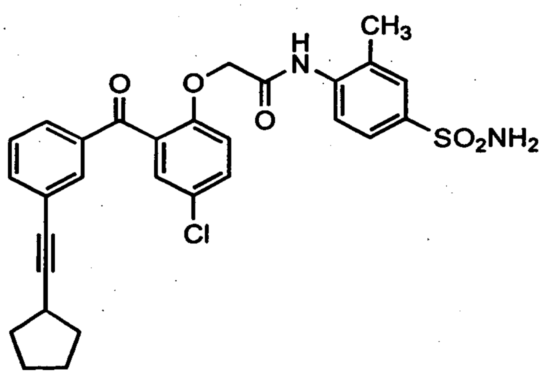
230

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **229** (1.5 g, 6.9 mmol), toluene (50 mL), and palladium on charcoal (0.15 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 7 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a crystalline material. The residue was washed several times with diethyl ether to afford **230** (1.3 g, >99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 2H), 6.65 (d, J= 8.4 Hz, 1H), 5.81 (s, 2H), 2.98 (s, 3H), 2.06 (s, 3H).

Step D:

Acid **225** (107 mg, 0.34 mmol), oxalyl chloride (0.032mL, 47mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (63 mg, 0.34 mmol), $NaHCO_3$ (143 mg, 1.7 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **227** (8 mg, 5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.73 (m, 6H), 7.60 (dd, J= 2.8, 8.8 Hz, 1H), 7.50 (t, J= 8 Hz, 1H), 7.46 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 4.79 (s, 2H), 4.29 (s, 1H), 3.27 (s, 3H), 2.18 (s, 3H). MS ES): 481 (M-H)$^-$.

<u>**Example 96**</u>



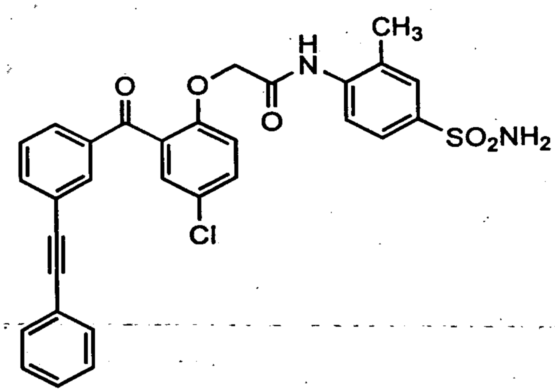
231

>99%). The product was used in the next step without further purification or characterization.

Step C:

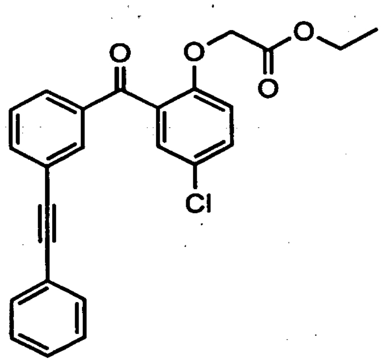
Acid **233** (140 mg, 0.37 mmol), oxalyl chloride (0.033mL, 48mg, 0.38 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (5 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (73 mg, 0.39 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **231** (88 mg, 43%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.61 (m, 8H), 7.44 (m, 2H), 7.21 (m, 2H), 4.77 (s, 2H), 2.81 (m, 1H), 2.14 (s, 3H), 1.93 (m, 2H), 1.58 (m, 6H).

Example 97



234

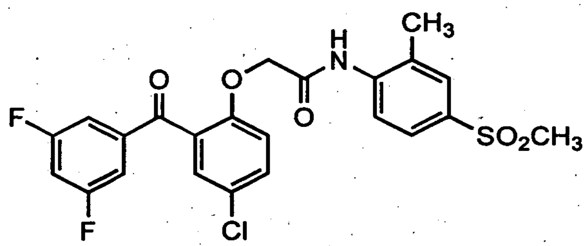
Step A:



235

afford **234** (10 mg, 11%) as a white solid. [1]H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.90 (s, 1H), 7.79 (m, 2H), 7.62 (m, 3H), 7.54 (m, 4H), 7.47 (d, J= 3 Hz, 1H), 7.38 (m, 3H), 7.22 (m, 3H), 4.80 (s, 2H), 2.15 (s, 3H).

Example 98

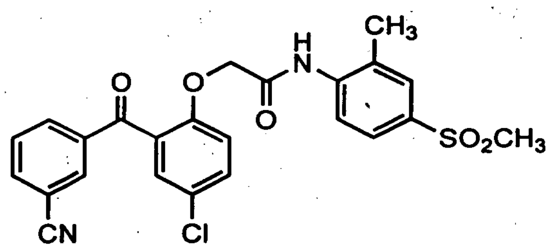


237

Step A:

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (69 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow oil was treated with pentanes to afford **237** (39 mg, 21%) as a pale yellow solid. [1]H NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.66 (m, 5H), 7.53 (d, J= 2.7 Hz, 1H), 7.49 (m, 2H), 7.25 (d, J= 9 Hz, 1H), 4.87 (s, 2H), 3.20 (s, 3H), 2.26 (s, 3H). MS (ES): 494 (M^+).

Example 99

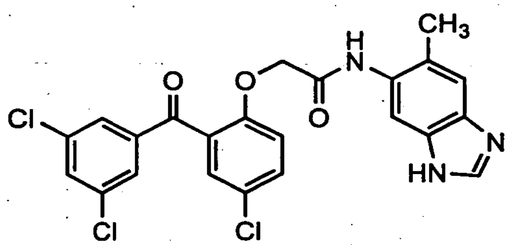


238

Acid **129** (120 mg, 0.38 mmol), oxalyl chloride (0.037 mL, 53 mg, 0.42 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (70 mg, 0.38

mmol), $NaHCO_3$ (155 mg, 1.9 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **240** (22 mg, 13%) as a pale yellow solid. At ambient temperature the product exists as a mixture of tautomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (m, 1H), 9.14 (m, 1H), 8.09 (s, 1H), 7.64 (d, J= 9 Hz, 1H), 7.50 (m, 4H), 7.23 (m, 2H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 456 (M^+), 457 $(M+H)^+$, 455$(M-H)^-$.

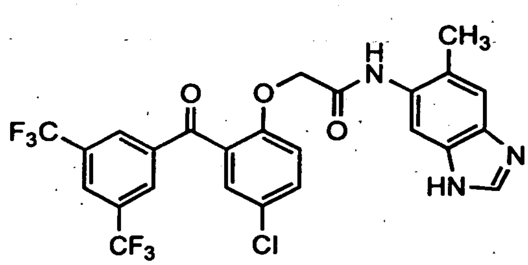
Example 102



241

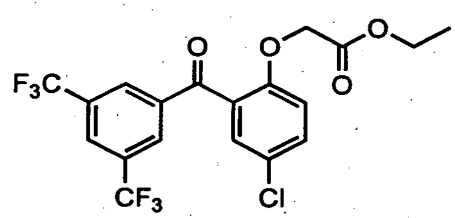
Acid **76** (120 mg, 0.33 mmol), oxalyl chloride (0.032 mL, 46 mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **210** (51 mg, 0.35 mmol), $NaHCO_3$ (139 mg, 1.7 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 2% MeOH:CH_2Cl_2 to afford **241** (11 mg, 7%) as a white solid. At ambient temperature the product exists as a mixture of tautomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 9.15 (m, 1H), 8.09 (s, 1H), 7.87 (m, 1H), 7.70 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 7.21 (m, 1H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 490 $(M+H)^+$, 488 $(M-H)^-$.

Example 103



Anisole **244** (3.76 g, 9.8 mmol), BBr_3 (29 mL of a 1.0 M soln. in CH_2Cl_2, 29 mmol), and CH_2Cl_2 (80 mL) were used according to general procedure IX to afford **245** (3.2 g, 89%) a pale green solid. The product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.40 (s, 1H), 8.21 (s, 2H), 7.48 (m, 2H), 6.98 (d, J= 8.8 Hz, 1H).

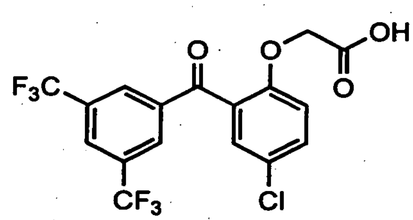
Step D:



246

Phenol **245** (3.2 g, 8.7 mmol), ethyl bromoacetate (1.1 mL, 1.6 g, 9.5 mmol), K_2CO_3 (3.0 g, 21.7 mmol), and acetone (50 mL) were used according to general procedure II to provide **246** (3.8 g, 97%) as a pale yellow solid. The product was used in the next step without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.31 (s, 2H), 7.68 (dd, J= 3, 9 Hz, 1H), 7.61 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 9 Hz, 1H), 4.79 (s, 2H), 4.06 (q, J= 7 Hz, 2H), 1.13 (t, J= 7 Hz, 3H).

Step E:

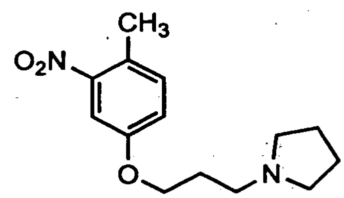


247

Ester **246** (3.8 g, 8.4 mmol), LiOH (0.88 g, 20.9 mmol) and a solution of THF, EtOH, and water (25 mL) were used according to general procedure III. The resulting white foam was treated with diethyl ether to afford **247** (3.1 g, 86%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 2H), 7.67 (dd, J= 3, 9 Hz, 1H), 7.58 (d, J= 3 Hz, 1H), 7.16 (d, J= 9 Hz, 1H), 4.63 (s, 2H).

(2.46 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J= 2.4 Hz, 1H), 7.37 (d, J= 8.4 Hz, 1H), 7.21 (dd, J= 2.4, 8.4 Hz, 1H), 4.11 (t, J= 6 Hz, 2H), 3.63 (t, J= 6 Hz, 2H), 2.38 (s, 3H), 2.22 (m, 2H).

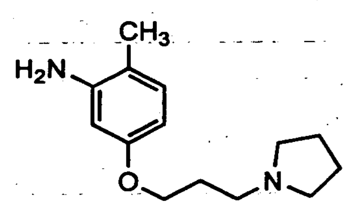
Step B:



250

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **249** (1.5 g, 5.47 mmol), pyrrolidine (0.91 mL, 0.78 g, 10.9 mmol), potassium carbonate (1.1 g, 8.2 mmol), and N, N-dimethylformamide (30 mL) and the mixture was allowed to stir at rt for 4 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **250** (1.24 g, 89%) as a brown oil. The product was used in the next step without further purification or characterization.

Step C:

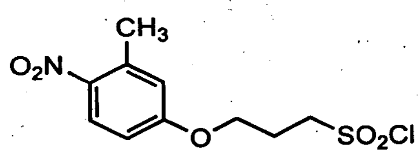


251

To a plastic-coated reaction vessel equipped with a stir bar, was added compound **250** (1.3 g, 4.9 mmol), absolute ethanol (20 mL), and palladium on charcoal (0.13 g of 10% Pd/C, 10% w/w). The vessel was placed on a hydrogenation apparatus at 60 p.s.i. for 3 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a dark oil. The residue was treated with a small amount of ethyl acetate and hexanes and the resulting precipitate was treated was filtered and the mother liquor was concentrated under reduced pressure to afford **251** (1.0

°C and 2-methyl-3-nitrophenol (30 g, 0.20 mol) was added dropwise as a solution in THF (100 mL). The reaction was then allowed to warm to rt, heated to 40 °C for 15 min., and then allowed to cool to rt. At this time, 1,3-propane sultone (25.6 g, 0.21 mol) in THF (100 mL) was added dropwise and the reaction was heated to reflux for 4-6 h. When judged to be complete, the reaction mixture was filtered and the resulting solid was washed with absolute ethanol and diethyl ether and dried in a vacuum oven. A solid precipitated out of the mother liquor, was filtered and washed with absolute ethanol and diethyl ether and dried in a vacuum oven to afford **253** (27 g, 46%) of a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J= 9 Hz, 1H), 7.05 (d, J= 2.7 Hz, 1H), 6.98 (dd, J= 2.7, 9.3 Hz, 1H), 4.22 (t, J= 6.6 Hz, 2H), 2.58 (m, 2H), 2.52 (s, 3H), 2.04 (m, 2H).

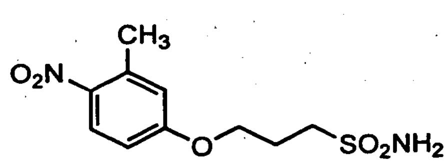
Step B:



254

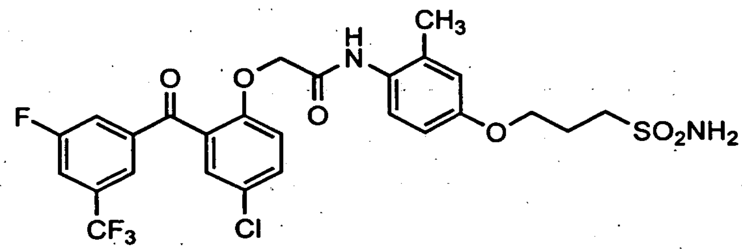
To a round-bottom flask equipped with a stir bar, an addition funnel, and nitrogen on demand was added the sulfonic acid salt **253** (11 g, 0.037 mol) and N,N-dimethylformamide (250 mL) and the reaction was cooled to 0 °C. Thionyl chloride (8.0 mL, 13.0 g, 0.11 mol) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 3 h. When judged to be complete, the reaction mixture was poured into a beaker of ice and the resulting white precipitate was filtered and placed in a vacuum oven to afford **254** (8.7 g, 80%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J= 9 Hz, 1H), 7.05 (d, J= 2.7 Hz, 1H), 6.98 (dd, J= 2.7, 9.3 Hz, 1H), 4.22 (t, J= 6.3 Hz, 2H), 2.61 (m, 2H), 2.57 (s, 3H), 2.04 (m, 2H).

Step C:



J= 2.8 Hz, 1H), 7.41 (m, 2H), 7.19 (d, J= 9.2 Hz, 1H), 7.11 (d, J= 8.4 Hz, 1H), 6.83 (s, 2H), 6.76 (d, J= 2.8 Hz, 1H), 6.69(dd, J=2.8, 8.4 Hz), 4.70 (s, 2H), 4.01 (t, J= 6.4 Hz, 2H), 3.08 (t, J= 8 Hz, 2H), 2.07 (m, 2H), 2.00 (s, 3H). MS (ES): 553 (M^+).

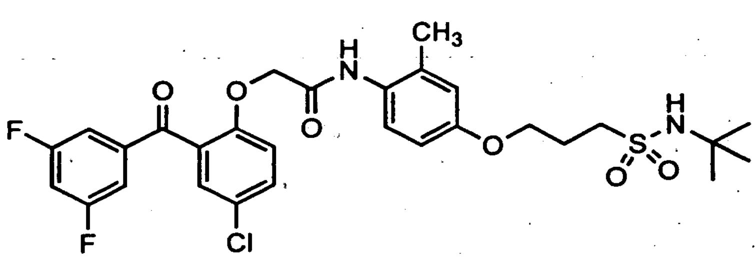
Example 106



257

Acid **71** (13 g, 0.035 mol), oxalyl chloride (7.0 mL, 9.8 g, 0.077 mol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (100 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **256** (7.81 g, 0.032 mol), $NaHCO_3$ (15 g, 0.18 mol), acetone (125 mL), and water (10 mL) were used according to general procedure VI. The product was crystallized from methanol to afford **257** (10.5 g, 50%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.05 (d, J= 8.4 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J= 2.7, 9 Hz, 1H), 7.57 (d, J= 2.7 Hz, 1H), 7.25 (d, J= 9 Hz, 1H), 7.13 (d, J= 9 Hz, 1H), 6.88 (s, 2H), 6.80 (d, J= 2.7 Hz, 1H), 6.73 (dd, J= 2.7, 9 Hz, 1H), 4.74 (s, 2H), 4.07 (t, J= 6 Hz, 2H), 3.13 (m, 2H), 2.13 (m, 2H), 2.03 (s, 3H). MS (ES): 602 $(M-H)^-$, 603 (M^+). Anal. Calcd for $C_{26}H_{23}N_2O_6ClF_4S$: C, 51.79; H, 3.84; N, 4.65. Found: C, 51.91; H, 3.88; N, 4.66.

Example 107

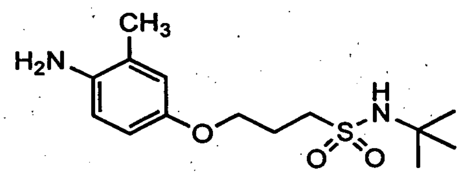


258

261

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added t-butylamine (0.33 mL, 0.23 g, 3.1 mmol), triethylamine (0.72 mL, 0.52 g, 5.2 mmol), and chloroform (20 mL). Sulfonyl chloride **260** (0.76 g, 2.6 mmol) in chloroform (3 mL) was added dropwise and the reaction was allowed to stir at rt for 2 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing $CHCl_3$ and water, the organics were collected, washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting brown residue was filtered through a pad of silica gel, eluding with hexanes to provide **261** (0.37 g, 43%) as a white solid. The product was used in the next step without further purification or characterization.

Step D:



262

To a plastic-coated reaction vessel equipped with a stir bar, was compound **261** (0.37 g, 1.1 mmol), ethanol (20 mL), and palladium on charcoal (37 mg of 10% Pd/C, 10w/w). The vessel was placed on a hydrogenation apparatus at 60 psig for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **262** (0.32 g, 95%) as brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (s, 1H), 6.85 (s, 1H), 6.53 (m, 1H), 6.49 (m, 1H), 4.51 (bs, 2H), 3.90 (t, J= 6 Hz, 2H), 3.09 (m, 2H), 2.08 (m, 2H), 1.99 (s, 3H), 1.22 (m, 9H).

Step E:

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **262** (111 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using

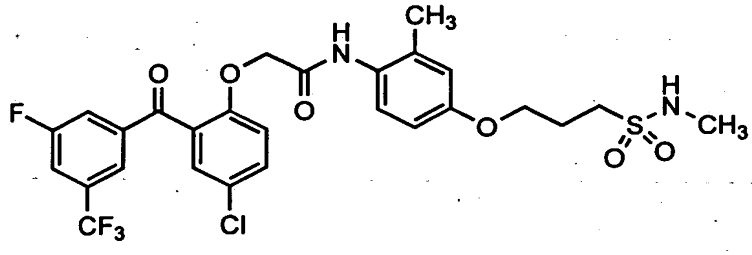
265

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **264** (2.1 g, 7.0 mmol), absolute ethanol (40 mL), and palladium on charcoal (0.21 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **265** (1.7 g, 90%) as a pale yellow solid. The product was used in the next step without further purification or characterization.

Step C:

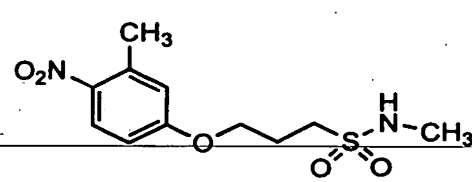
Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **265** (78 mg, 0.29 mmol), $NaHCO_3$ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The resulting residue was treated several times with pentane to afford **263** (90 mg, 45%) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.98 (d, J= 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J= 2.4, 8.8 Hz, 1H), 7.51 (d, J= 2.8 Hz, 1H), 7.20 (d, J= 8.8 Hz, 1H), 7.08 (d, J= 8.8 Hz, 1H), 6.76 (d, J= 2.4 Hz, 1H), 6.68 (dd, J= 2.8, 8.8 Hz, 1H), 4.69 (s, 2H), 4.00 (t, J= 6 Hz, 2H), 3.13 (m, 2H), 2.75 (s, 6H), 2.05 (m, 2H), 1.98 (s, 3H). MS (ES): 631 (M^+)

<u>Example 109</u>



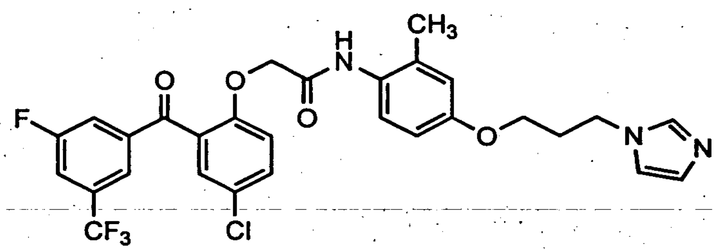
266

Step A:



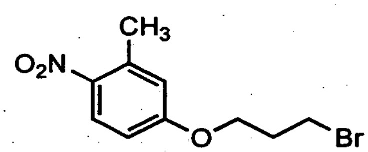
hexanes to afford **266** (80 mg, 41%) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.98 (d, J= 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J= 2.4, 8.8 Hz, 1H), 7.52 (d, J= 2.8 Hz, 1H), 7.20 (d, J= 9.2 Hz, 1H), 7.08 (d, J= 8.4 Hz, 1H), 6.94 (q, J= 5 Hz, 1H), 6.74 (d, J= 2.8 Hz, 1H), 6.68 (dd, J= 2.8, 8.8 Hz, 1H), 4.68 (s, 3H), 4.00 (m, 2H), 3.10 (t, J= 8 Hz, 2H), 2.54 (d, J= 5 Hz), 2.01 (m, 5H). MS (ES): 617 (M^+).

<u>**Example 110**</u>



269

Step A:



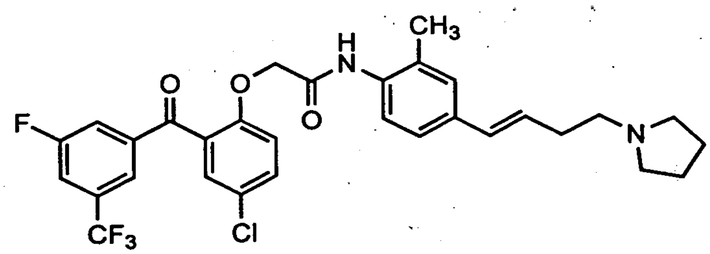
270

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-methyl-3-nitrophenol (5.0 g, 0.033 mol), dibromopropane (26 mL, 52.7 g, 0.26 mol), potassium carbonate (6.8 g, 0.05 mol), and N, N-dimethylformamide (100 mL) and the mixture was allowed to stir at rt for 2.5 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting oil was distilled to afford **270** (8.0 g, 89%) a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J= 9.2 Hz, 1H), 7.02 (d, J= 2.8 Hz, 1H), 6.96 (dd, J= 2.4, 8.8 Hz, 1H), 4.16 (t, J= 6 Hz, 2H), 3.63 (t, J= 6 Hz, 2H), 2.51 (s, 3H), 2.24 (m, 2H).

Step B:

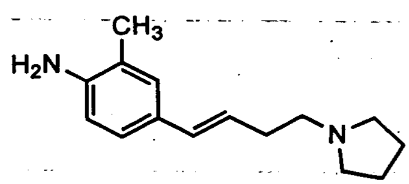
Acid 71 (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **272** (67 mg, 0.29 mmol), $NaHCO_3$ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ as eluant to afford **269** (84 mg, 45%) as a pink solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.05 (d, J= 9 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J= 3, 9 Hz, 1H), 7.65 (s, 1H), 7.57 (d, J= 3Hz, 1H), 7.24 (m, 2H), 7.13 (d, J= 6Hz, 1H), 6.92 (s, 1H), 6.79 (d, J=3 Hz, 1H), 6.73 (dd, J= 3, 9 Hz, 1H), 4.74 (s, 2H), 4.14 (t, J= 6Hz, 2H), 3.88 (t, J= 6Hz, 2H), 2.16 (m, 2H), 2.03 (s, 3H). MS (ES): 589 (M^+), 590 $(M+H)^+$.

Example 111



272

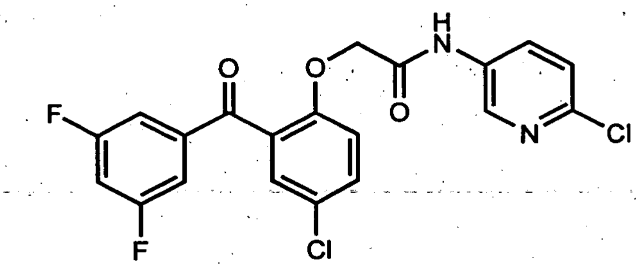
Step A:



273

To a sealed-tube reaction vessel equipped with a stir bar and nitrogen on demand was added 4-bromo-2-methyl aniline (0.8 g, 4.3 mmol), palladium (II) acetate (97 mg, 0.43 mmol), tri-o-tolylphosphine (0.52 g, 1.72 mmol), N,N-dimethylformamide (15 mL), N-butylenepyrrolidine (2.7 g, 21.5 mmol), and triethylamine (4.2 mL, 3.0 g, 30.1 mmol). The tube was sealed and allowed to stir at 80 °C for 18 h. When judged to be complete, the reaction was filtered through a pad of celite and the filtrate was poured into ethyl acetate and water. The organics were collected and washed with water and brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product

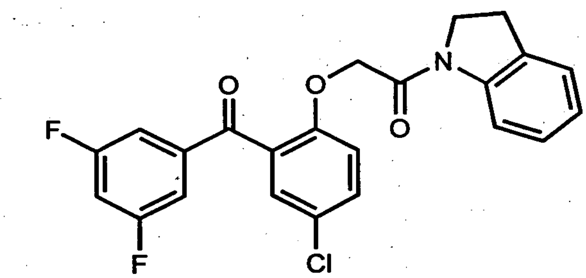
Example 113



275

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-2-methoxypyridine (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by trituration with ether gave **275** (0.134 g, 70%): mp 198-200 °C; MS (ES+) *m/z* 437 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 8.80 (d, 1 H), 8.30 (dd, 1 H), 7.58 (dd, 1 H), 7.41 (dd, 1 H), 7.39-7.38 (m, 2 H), 7.32 (d, 1 H), 7.15-7.11 (m, 1 H), 7.07 (d, 1 H), 4.76 (s, 2 H).

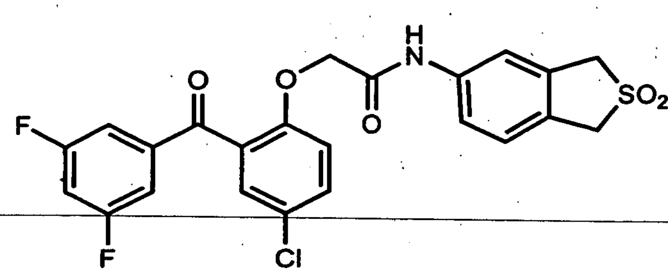
Example 114



276

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and indoline (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by crystallization from methylene chloride/hexane gave **276** (0.069 g, 37%): mp 158-160 °C; MS (ES+) *m/z* 428 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1 H), 7.44-7.39 (m, 4 H), 7.22-7.18 (m, 2 H), 7.07-6.97 (m, 3 H), 4.70 (s, 2 H), 3.98 (t, 2 H), 3.18 (t, 2 H) ppm.

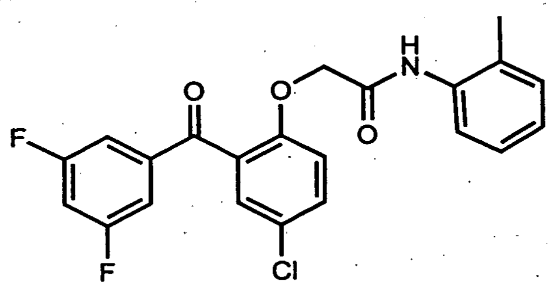
Example 115



279

The title compound was prepared according to General Procedure VI from acid **49** (0.49 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.035 mL, 0.41 mmol). Isolation by flash chromatography using 15% ethyl acetate/hexane as eluant followed by trituration with hexanes gave **279** (0.072 g, 40%) in ca. 80% purity: MS (ES+) *m/z* 442 (M+H), 464 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 1 H), 7.34-7.27 (m, 3 H), 7.19-7.15 (m, 2 H), 7.13-7.08 (m, 2 H), 7.02-6.93 (m, 2 H), 4.70 (s, 2 H), 4.65 (s, 1 H), 4.46 (s, 1 H), 3.73 (t, 1 H), 3.57 (t, 1 H), 2.81-2.75 (m, 2 H).

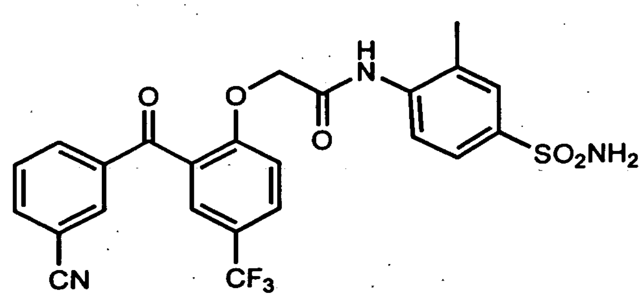
Example 118



280

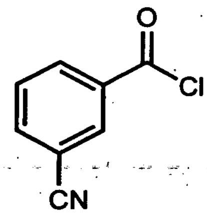
The title compound was prepared according to General Procedure VI from acid **49** (0.50 mmol) and *o*-toluidine (0.05 mL, 0.43 mmol). Isolation by flash chromatography using 10% ethyl acetate/hexane as eluant gave **280** (0.121 g, 58%): MS (ES+) *m/z* 416 (M+H), 438 (M+Na); MS (ES-) *m/z* 414 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.71 (d, 1 H), 7.53 (dd, 1 H), 7.36 (d, 1 H), 7.34-7.31 (m, 2 H), 7.22-7.17 (m, 2 H), 7.09 (app t, 1 H), 7.05 –7.01 (m, 2 H), 4.77 (s, 2 H), 2.18 (s, 3 H) ppm.

Example 119



281

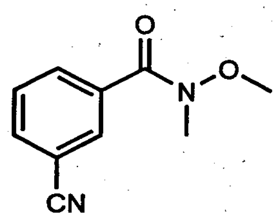
Step C:



284

Oxalyl chloride (48 mL, 96.5 mmol) was added dropwise over 1 h to a solution of 3-cyanobenzoic acid (5.767 g, 38.6 mmol) in 200 mL of CH_2Cl_2 and 0.10 mL of DMF, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* to give **284** (8.516 g), which was used immediately without further purification or characterization.

Step D:

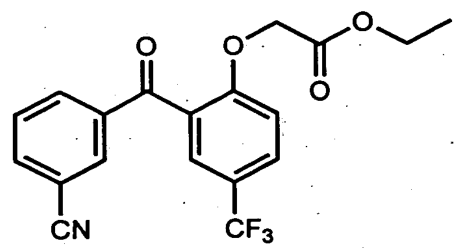


285

A solution of N,O-dimethylhydroxylamine (4.90 g, 50.2 mmol) in 20 mL of triethylamine and 100 mL of chloroform was cooled to 0 °C, and **284** (8.52 g, 38.6 mmol) was added dropwise over 10 min. The resulting mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature over 1.25 h. The reaction mixture was diluted with 150 mL ethyl acetate and washed with two 100-mL portions of water and a small portion of brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 285 (6.381 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.95 (d, 1 H), 7.75 (d, 1 H), 7.55 (dd, 1 H), 3.54 (s, 3 H), 3.39 (s, 3 H).

Step E:

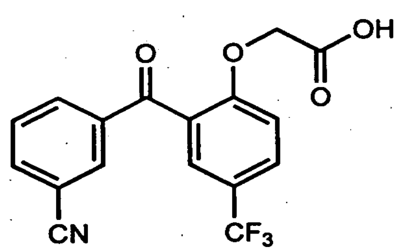
Step G:



288

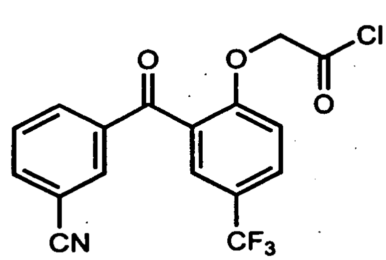
The title compound (2.196 g, 100%) was prepared according to General Procedure II from the phenol derivative **287** (1.78 g, 5.91 mmol). This intermediate was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 8.09 (d, 1 H), 7.82 (d, 1 H), 7.74 (d, 1 H), 7.73 (s, 1 H), 7.58 (t, 1 H), 6.90 (d, 1 H), 4.58 (s, 2 H), 4.20 (q, 2 H), 1.24 (t, 3 H).

Step H:

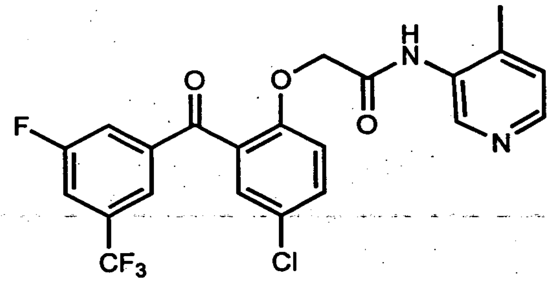


289

The title compound (1.758 g, 85%) was prepared according to General Procedure III from the ester derivative **288** (2.2 g, 5.91 mmol). This intermediate was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 8.11 (d, 1 H), 7.90 (d, 1 H), 7.78 (dd, 1 H), 7.69 (d, 1 H), 7.64 (t, 1 H), 7.12 (d, 1 H), 4.86 (s, 2 H).

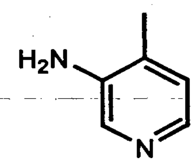


Example 121



292

Step A:



293

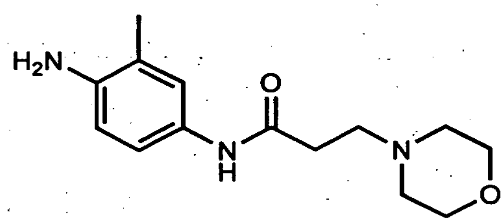
A mixture of 4-methyl-3-nitropyridine (1.102 g, 7.24 mmol) and 10% palladium on carbon (0.096 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 49 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **293** (0.849 g, quant.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.92 (d, 1 H), 6.93 (d, 1 H), 3.59 (br s, 2 H), 2.14 (s, 3 H).

Step B:

Compound **292** was prepared according to the General Procedure IV from the acid 71 (0.188 g, 0.5 mmol) and the aminopyridyl derivative **293** (0.065 g, 0.6 mmol). Purification by flash chromatography using 0.5-2% methanol/methylene chloride as eluant gave **292** (0.071 g, 30%) as a white solid: MS (ES+) *m/z* 467 (M+H); MS (ES-) *m/z* 465 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.65 (s, 1 H), 8.35 (d, 1 H), 7.88 (s, 1 H), 7.70 (d, 1 H), 7.62-7.58 (m, 2 H), 7.40 (d, 1 H), 7.16 (d, 1 H), 7.10 (d, 1 H), 4.76 (s, 2 H), 2.26 (s, 3 H) ppm.

vacuo, suspended in ethyl acetate, and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, and allowed to crystallize. The crystalline impurity was removed by filtration, and the filtrate was concentrated *in vacuo* to give **296** (1.767 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (br s, 1 H), 8.03 (d, 1 H), 7.54 (d, 1 H), 7.43 (dd, 1 H), 3.84-3.82 (m, 4 H), 2.76-2.73 (m, 2 H), 2.64 (br s, 4 H), 2.62 (s, 3 H), 2.58-2.55 (m, 2 H) ppm.

Step C:



297

A mixture of compound **296** (0.202 g, 0.69 mmol) and 10% palladium on carbon (0.018 g) in 10 mL of methanol was stirred at room temperature under an atmosphere of 53 psi hydrogen gas for 2.17 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **297** (0.192 g, quant.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (br s, 1 H), 7.38 (s, 1 H), 7.27 (dd, 1 H), 6.76 (s, 1 H), 3.97-3.92 (m, 4 H), 2.91-2.83 (m, 2 H), 2.77-2.72 (m, 4 H), 2.66-2.62 (m, 2 H), 2.25 (s, 3 H).

Step D:

Compound **294** was prepared according to the General Procedure VI from the acid chloride **49** (0.5 mmol) and the aniline derivative **297** (0.180 g, 0.68 mmol). Purification by flash chromatography using 1-2% methanol/methylene chloride as eluant gave **294** (0.203 g, 71%): MS (ES-) *m/z* 570 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1 H), 8.27 (s, 1 H), 7.57 (d, 1 H), 7.52-7.48 (m, 2 H), 7.35 (d, 1 H), 7.31-7.30 (m, 2 H), 7.22-7.20, (d, 1 H), 7.04-7.00 (m, 2 H), 4.64 (s, 2 H), 3.77 (br s, 4 H), 2.71-2.68 (m, 2 H), 2.57 (br s, 4 H), 2.50-2.47 (m, 2 H), 2.14 (s, 3 H).

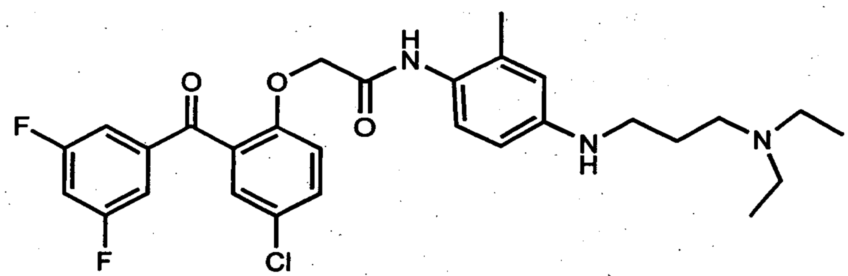
<u>**Example 123**</u>

hydrogen gas for 1 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **300** (0.166 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.07 (s, 1 H), 6.92 (s, 1 H), 6.58 (d, 1 H), 6.40 (d, 1 H), 6.36 (dd, 1 H), 4.08 (t, 2 H), 3.49-3.48 (m, 1 H), 3.26 (br s, 2 H), 3.08-3.05 (m, 2 H), 2.13 (s, 3 H), 2.08-2.02 (m, 2 H).

Step C:

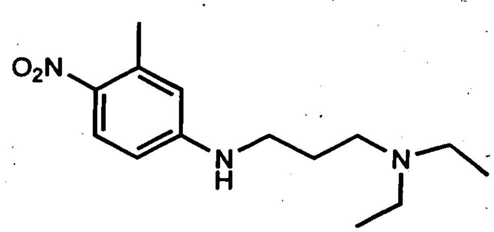
Compound **298** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **300** (0.155 g, 0.67 mmol). Purification by flash chromatography using 2% methanol/methylene chloride as eluant gave **298** (0.219 g, 68%): MS (ES+) *m/z* 539 (M+H); MS (ES-) *m/z* 537 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.55 (dd, 1 H), 7.49 (s, 1 H), 7.39 (d, 1 H), 7.35-7.31 (m, 2 H), 7.30 (d, 1 H), 7.08 (s, 1 H), 7.06-7.01 (m, 2 H), 6.93 (s, 1 H), 6.43-6.40 (m, 2 H), 4.67 (s, 2 H), 4.09-4.06 (m, 2 H), 3.54 (br s, 1 H), 3.11 (t, 2 H), 2.11-2.06 (m, 5 H).

Example 124



301

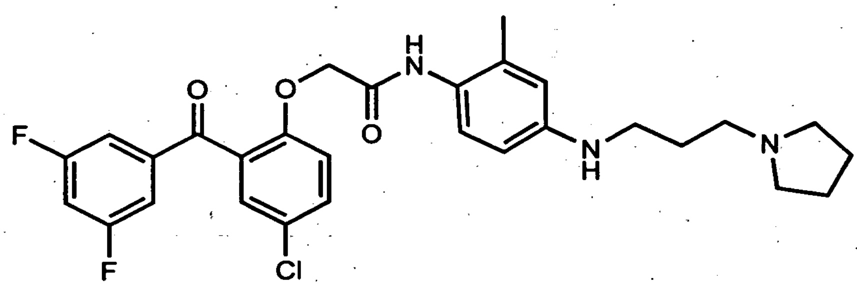
Step A:



302

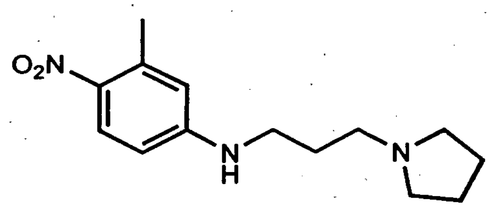
s, 1 H), 7.54 (dd, 1 H), 7.39 (d, 1 H), 7.34-7.31 (m, 2 H), 7.25 (d, 1 H), 7.05-6.99 (m, 2 H), 6.43-6.41 (m, 2 H), 4.65 (s, 2 H), 3.15 (t, 2 H), 2.57-2.52 (m, 6 H), 2.07 (s, 3 H), 1.80-1.73 (m, 2 H), 1.05 (t, 6 H).

Example 125



304

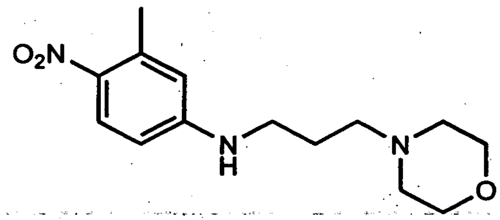
Step A:



305

A mixture of 5-fluoro-2-nitrotoluene (0.37 mL, 3.0 mmol), 1-(3-aminopropyl)pyrrolidine (0.64 mL, 5.1 mmol), and sodium bicarbonate (0.454 g, 5.4 mmol) in 7.5 mL of pyridine and 0.75 mL of water was heated to reflux for 3 h. The reaction mixture was stirred at room temperature an additional 3 h, then partitioned between 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with an additional 20 mL of ethyl acetate, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.758 g of crude material. Purification by flash chromatography using 0.5-10% methanol/methylene chloride as eluant gave **305** (0.595 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H), 6.35 (dd, 1 H), 6.29 (d, 1 H), 6.09 (br s, 1 H), 3.30-3.26 (m, 2 H), 2.65-2.62 (m, 2 H), 2.61 (s, 3 H), 2.58-2.52 (m, 4 H), 1.86-1.78 (m, 6 H).

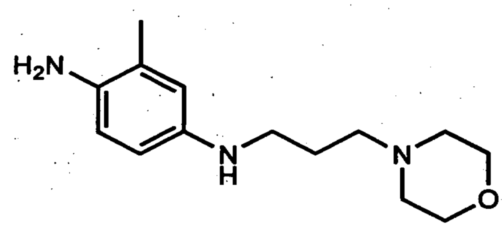
Step A:



308

A mixture of 5-fluoro-2-nitrotoluene (0.24 mL, 2.0 mmol), 4-(3-aminopropyl)morpholine (0.50 mL, 3.4 mmol), and sodium bicarbonate (0.302 g, 3.6 mmol) in 5 mL of pyridine and 0.5 mL of water was heated to reflux for 1 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.493 g of crude material. Purification by flash chromatography using 1% methanol/methylene chloride as eluant gave **308** (0.279 g, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H), 6.38 (dd, 1 H), 6.31 (s, 1 H), 5.92 (br s, 1 H), 3.77-3.75 (m, 4 H), 3.31-3.27 (m, 2 H), 2.6 (s, 3 H), 2.54-2.50 (m, 6 H), 1.85-1.79 (m, 2 H).

Step B:



309

A mixture of compound **308** (0.266 g, 0.95 mmol) and 10% palladium on carbon (0.020 g) in 5 mL of methanol was stirred at room temperature under an atmosphere of 60 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **309** (0.229 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, 1 H), 6.43 (d, 1 H), 6.39 (dd, 1 H), 3.74-3.72 (m, 4 H), 3.14-3.11 (m, 2 H), 2.48-2.45 (m, 6 H), 2.14 (s, 3 H), 1.81-1.75 (m, 2 H).

Step C:

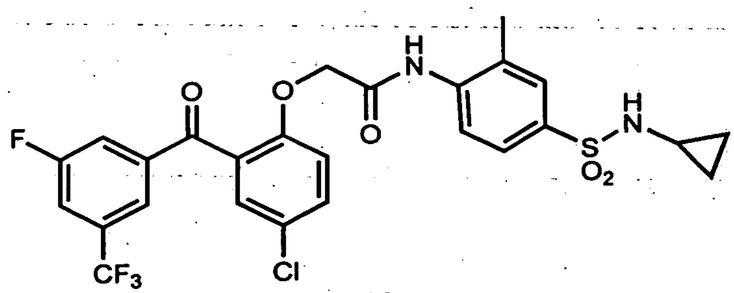
312

A mixture of compound **311** (0.308 g, 1.2 mmol), 1.5 M HCl (2.5 mL), and ethanol (12 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 1 h. The reaction mixture was poured into 50 mL saturated $NaHCO_3$ (aq) and extracted with two 30-mL portions of methylene chloride. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **312** (0.337 g), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 6.68 (d, 1 H), 4.29 (t, 1 H), 4.07 (br s, 2 H), 3.00-2.93 (m, 2 H), 2.18 (s, 3 H), 1.10 (t, 3 H).

Step C:

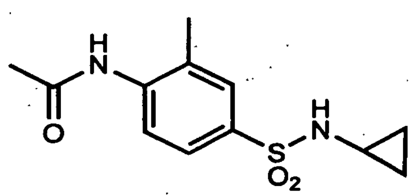
Compound **310** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aniline derivative **312** (0.169 g, 0.6 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave **310** (0.016 g, 6%): MS (ES+) *m/z* 573 (M+H); MS (ES-) *m/z* 571 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1 H), 8.08 (d, 1 H), 7.88 (s, 1 H), 7.69 (m, 3 H), 7.59 (dd, 2 H), 7.38 (d, 1 H), 7.09 (d, 1 H), 4.74 (s, 2 H), 3.03-2.95 (m, 2 H), 2.31 (s, 3 H), 1.11 (t, 3 H).

<u>**Example 128**</u>

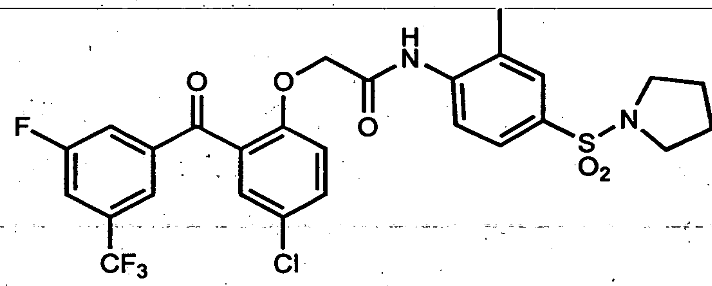


313

Step A:

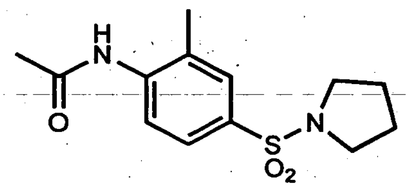


Example 129



316

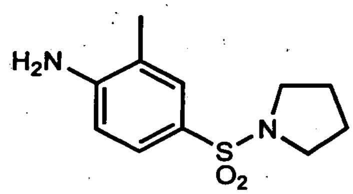
Step A:



317

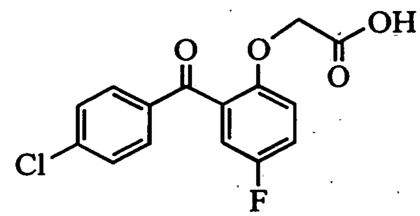
A mixture of sulfonyl chloride **464** (1.10 g, 4.4 mmol), pyrrolidine (0.55 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 6 d. The reaction mixture was then filtered, and the filter cake was washed with methylene chloride and methanol and dried with a vacuum pump to give **317** (0.696 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 7.82 (d, 1 H), 7.60 (d, 1 H), 7.55 (dd, 1 H), 3.10-3.07 (m, 4 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 1.64-1.58 (m, 4 H).

Step B:



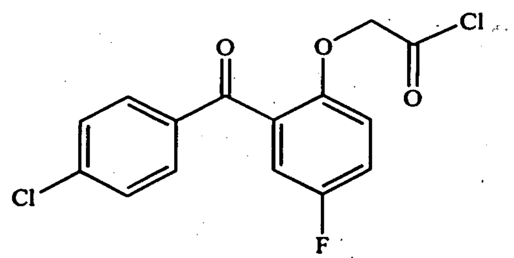
318

A mixture of compound **317** (0.690 g, 2.44 mmol), 1.5 M HCl (5.0 mL), and ethanol (25 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 7 h. The reaction mixture was filtered to give **318** (0.369 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2 H), 6.64 (d, 1 H), 5.73 (br s, 2 H), 3.01-2.98 (m, 4 h), 2.05 (s, 3 H), 1.60-1.56 (m, 4 H).



322

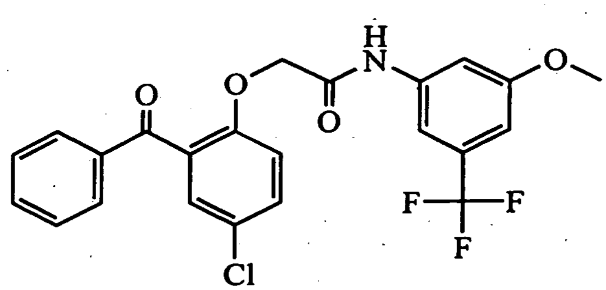
Ester **321** (6.72 g, 20 mmol), ethanol (80 mL), water (20 mL), and lithium hydroxide monohydrate (1 g, 24 mmol) were used as in general procedure III to afford carboxylic acid **322** as off-white solid (6.56 g, crude material). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.1 (d, 1H), 7.3 (d, 1H), 7.4 (m, 1H), 7.6 (d, 2H), 7.8 (d, 2H), 13 (bs, 1H); MS (ES$^-$) *m/z* 307 (M-H)$^-$.



323

Into a round-bottom flask were placed acid **322** (3 g, 10 mmol) and thionyl chloride (51 mL of a 2N solution in methylene chloride, 102 mmol). After refluxing for 1 1/2 h, the mixture was concentrated in vacuo to give **323** as a dark purple oil, which was used without characterization or purification.

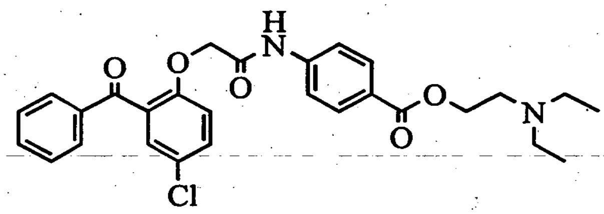
Example 130



324

4-Aminophenyl acetonitrile (Aldrich, 0.214 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate with 0.01% NEt_3 to afford **326** as an orange solid (0.26 g, 40%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4 (s, 2H), 4.7 (s, 2H), 7.2 (d, 1H), 7.3 (d, 2H), 7.45 (s, 1H), 7.5-7.6 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.9 (s, 1H); MS (ES$^-$) *m/z* 403 (M-H)$^-$.

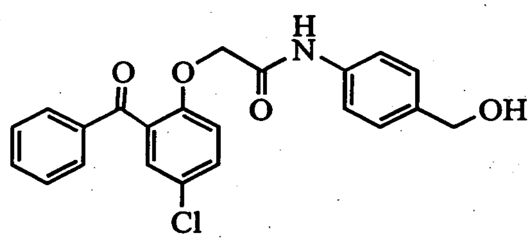
Example 133



327

Procaine (ICN, 0.382 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.38 g, 1.24 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 24:1 methylene chloride:methanol to afford **327** as an off-white solid (0.037 g, 4.5%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1 (t, 6H), 2.8 (bs, 2H), 4.3 (bs, 2H), 4.8 (bs, 2H), 7.2 (d, 1H), 7.5-7.7 (m, 8H), 7.8 (d, 2H), 7.9 (d, 2H), 10.2 (s, 1H); MS (AP$^+$) *m/z* 509 (M+H)$^+$.

Example 134

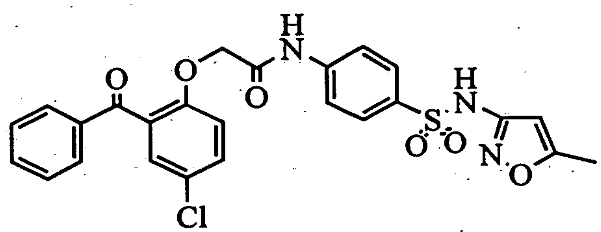


328

4-Amino benzyl alcohol (Fluka, 0.2 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **328** as a dark yellow solid (0.06 g, 10%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.45 (d, 2H), 4.7 (s, 2H), 5.1 (t, 1H), 7.2 (t, 3H), 7.45 (t, 3H), 7.55 (t, 2H), 7.6 (t, 2H), 7.8 (d, 2H), 9.7 (s, 1H); MS (ES$^-$) *m/z* 394 (M-H)$^-$.

11%). [1]H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 7.15 (dd, 1H), 7.2 (s, 2H), 7.25 (d, 1H), 7.35 (t, 1H), 7.5 (d, 2H), 7.65 (d, 2H), 9.87 (bs, 2H), 10.25 (s, 1H); MS (ES$^-$) *m/z* 461 (M-H)$^-$.

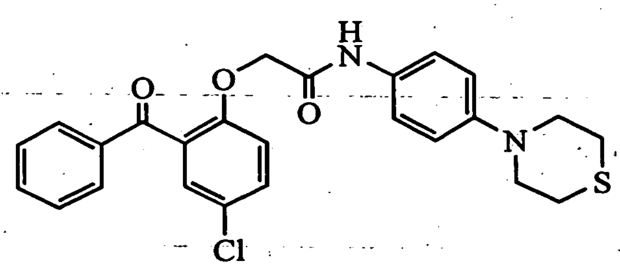
Example 137



331

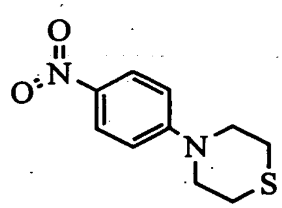
Sulfamethoxazole (Aldrich, 0.424 g, 1.67 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (5 mL), and acid chloride **320** (0.52 g, 1.68 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 3:2 hexanes:ethyl acetate as elutant to afford **331** as an off-white solid (0.021 g, 2.4%). [1]H NMR (DMSO-d_6, 400 MHz) δ 2.3 (s, 3H), 4.7 (s, 2H), 6.1 (s, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.45 (d, 2H), 7.55 (m, 2H), 7.7 (d, 2H), 7.8 (d, 4H), 10.3 (s, 1H), 11.3 (s, 1H); MS (ES$^-$) *m/z* 524 (M-H)$^-$.

Example 138

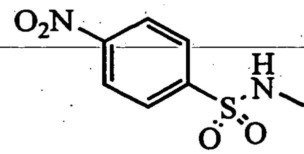


332

Step A:



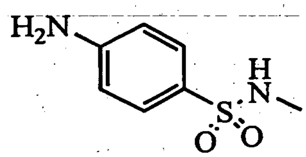
333



336

4-Nitrobenzenesulfonylchloride (Aldrich, 44.3 g, 200 mmol) was added portionwise to a solution of methylamine in ethanol (250 mL, 208 mmol) which was stirred at 0 °C under nitrogen. After removing the ice bath, the reaction was stirred for 45 min. Water (250 mL) was added and the resulting product was filtered to afford **336** as a crystalline solid (37.6 g, 87%). The crude material was used without purification.

Step B:



337

Palladium on carbon (2 g, 10% w/w) was added to a solution of compound **336** (17.3 g, 80 mmol), methanol (80 mL), THF (80 mL), and hydrochloric acid (concentrated, 7 mL, 84 mmol) and used as in general procedure XII to afford **337** as a white solid (14.3 g, 80%). The crude material was used without purification.

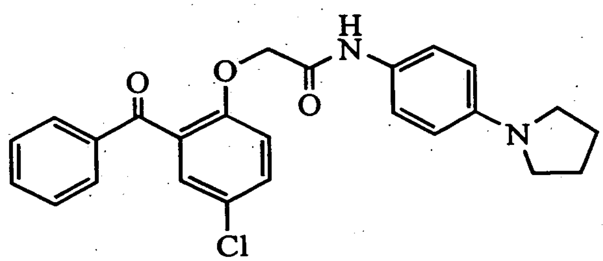
Step C:

Compound **337** (0.32 g, 1.44 mmol), NEt_3 (0.5 mL, 3.6 mmol), acetonitrile (5 mL), and acid chloride **320** (0.444 g, 1.44 mmol) in acetonitrile (5 mL) were used as in general procedure X. After 6 d, another equivalent of acid chloride **320** (0.444 g, 1.44 mmol) was added and the solution was stirred. The reaction mixture was filtered and the resulting solid was washed with acetonitrile and water, and suspended in ethyl acetate. The suspension was filtered and the filtrate concentrated in vacuo to afford **335** as an off-white solid (0.152 g, 23%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.3 (d, 3H), 4.7 (s, 2H), 7.15 (d, 1H), 7.3 (m, 1H), 7.45 (s, 1H), 7.5 (t, 2H), 7.54-7.62 (m, 2H), 7.7 (s, 4H), 7.8 (d, 2H), 10.2 (s, 1H); MS (ES$^-$) *m/z* 457 (M-H)$^-$.

<u>**Example 140**</u>

Compound **340** (0.85 g, 4.6mmol), NEt_3 (0.87 mL, 6.2 mmol), acetonitrile (8 mL), and acid chloride **320** (1.29 g, 4.2 mmol) in acetonitrile (8 mL) were used as in general procedure X. After 2 d, water was added and the resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using 35% ethyl acetate in hexanes to afford **338** as an off-white/ pale yellow solid (0.480 g, 23%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.95 (s, 3H), 4.7 (s, 2H), 7.15 (d, 2H), 7.2 (d, 1H), 7.45 (d, 3H), 7.7 (m, 7H), 7.85 (d, 2H), 9.6 (s, 1H), 9.8 (s, 1H); MS (ES$^-$) *m/z* 457 (M-H)$^-$.

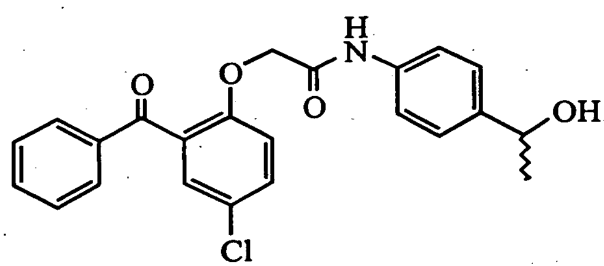
Example 141



341

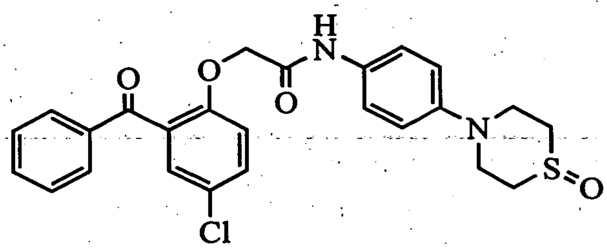
4-(N-pyrrolidine)aniline (Apin, 0.262 g, 1.61 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **341** as an off-white solid (0.112 g, 16%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2 (t, 4H), 3.2 (t, 4H), 4.66 (s, 2H), 6.5 (d, 2H), 7.2 (s, 1H), 7.3 (t, 2H), 7.45 (s, 1H), 7.5 (t, 2H), 7.6 (m, 2H), 7.8 (d, 2H), 9.3 (s, 1H); MS (ES$^-$) *m/z* 433 (M-H)$^-$.

Example 142



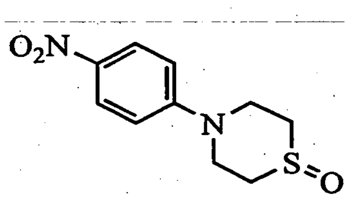
342

Example 144

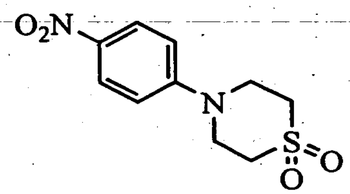


344

Step A:



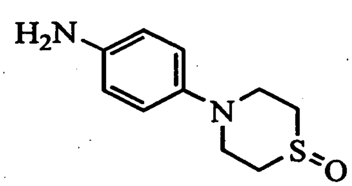
345



346

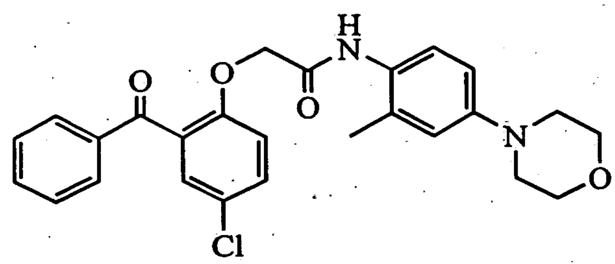
3-Chloroperoxybenzoic acid (~60%, 20.3 g, 70.6 mmol) in methylene chloride was added dropwise to a cooled solution of compound **333** (11.5 g, 51.1 mmol) in methylene chloride (250 mL total reaction volume) and stirred at –78 °C. After 2 h, the reaction was warmed to rt and stirred overnight. The reaction mixture was washed with saturated sodium meta bisulfite, 2N NaOH, and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of **345** and **346** as a yellow solid (8.47 g, crude material). The crude material was used without purification.

Step B:



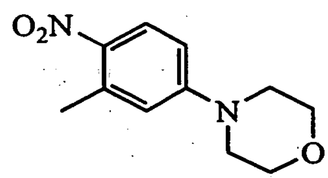
347

The mixture of **345** and **346** (8.47 g, 35.3 mmol), palladium on carbon (1.4 g, 10% w/w), ethanol (100 mL) and THF (50 mL) were used as in general procedure XII using 60 psi of hydrogen. The product was purified by flash chromatography using a gradient between



349

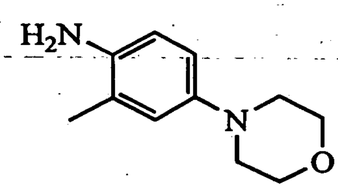
Step A:



350

4-Chloro-2-nitrotoluene (SALOR, 2 g, 11.7 mmol) in pyridine (25 mL), sodium bicarbonate (2 g, 23.8 mmol), water (5 mL), and morpholine (Aldrich, 2.03 g, 23.3 mmol) were used as in general procedure XI to afford **350** as a yellow solid (0.804 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.5 (s, 3H), 3.4 (t, 4H), 3.7 (t, 4H), 6.9 (d, 2H), 8 (d, 1H). The crude material was used without purification.

Step B:



351

Compound **350** (0.72 g, 4.63 mmol), palladium on carbon (0.1 g, 10% w/w), ethanol (20 mL), and THF (20 mL) were used as in general procedure XII using 50 psi of hydrogen to afford **351** as a brown solid (0.623 g, crude material).

Step C:

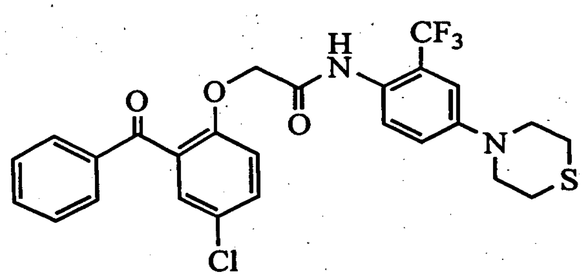
354

Compound **353** (1.62 g, 5.9 mmol), palladium on carbon (0.2 g, 10% w/w), ethanol (12 mL) and THF (12 mL) were used as in general procedure XII using 75 psi of hydrogen to afford **354** as a brown solid (1.41 g, crude material).

Step C:

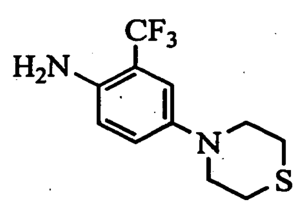
Compound **354** (1.41 g, 5.73 mmol), NEt_3 (0.8 mL, 5.74 mmol), acetonitrile (15 mL), and acid chloride **320** (1.8 g, 5.82 mmol) in acetonitrile (15 mL) were used as in general procedure X. The product was purified by flash chromatography using 35% ethyl acetate in hexanes and further purified by flash chromatography using 1:1 ethyl acetate:hexanes to afford **352** as an off-white solid (0.426 g, 14%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.2 (t, 4H), 3.75 (t, 4H), 4.7 (s, 2H), 7.15 (s, 1H), 7.2 (m, 3H), 7.45-7.55 (m, 3H), 7.6 (t, 2H), 7.8 (d, 2H), 9 (s, 1H); MS (ES$^-$) m/z 517 (M-H)$^-$.

Example 148



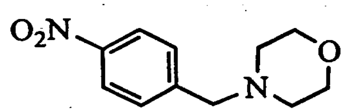
355

Step A:



356

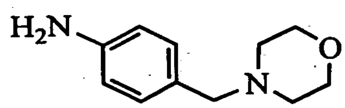
5-Bromo-2-nitrobenzotrifluoride (Lancaster, 2 g, 7.4 mmol) in pyridine (20 mL), sodium bicarbonate (1.25 g, 14.9 mmol), water (5 drops), and thiomorpholine (Aldrich, 1.52 g, 14.7 mmol) were used as in general procedure XI to afford **356** as a yellow solid (1.63 g,



359

Morpholine (Aldrich, 0.74 mL, 8.5 mmol) was added dropwise to a solution of 4-nitro-benzylbromide (Aldrich, 2 g, 9.26 mmol), in acetone (20 mL), and potassium carbonate (2.4 g, 17.4 mmol). The resulting suspension was stirred at rt for 6 d under nitrogen. The mixture was filtered and the filtrate was concentrated in vacuo to afford **359** as a pale yellow solid (1.89 g, crude material).

Step B:



360

Compound **359** (1.89 g, 4.63 mmol), palladium on carbon (0.325 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 50 psi of hydrogen to afford **360** as a brown solid (1.6 g, crude material).

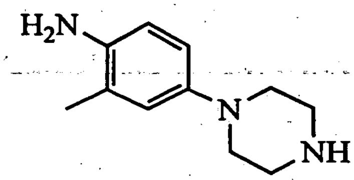
Step C:

Compound **360** (1.6 g, 8.3 mmol), NEt_3 (0.95 mL, 6.8 mmol), acetonitrile (7 mL), and acid chloride **320** (1.53 g, 4.95 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate **358** as an off-white solid (0.264g, 12%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.35 (d, 4H), 3.41 (s, 3H), 3.57 (t, 4H), 4.73 (s, 2H), 7.23 m, 3H), 7.47-7.67 (m, 7H), 7.83 (d, 2H), 9.78 (s, 1H); MS (ES$^-$) *m/z* 463 (M-H)$^-$.

<u>**Example 150 and Example 151**</u>

in vacuo to afford **363** as a yellow solid (4.22 g). MS (ES^+) *m/z* 222 $(M+H)^+$. The crude product was used without purification.

Step B:



364

Compound **363** (1.88 g, 8.5 mmol), palladium on carbon (0.563 g, 10% w/w), ethanol (35 mL), and THF (35 mL) were used as in general procedure XII to afford **364** as a yellow oil (1.7 g). The crude product was used without purification.

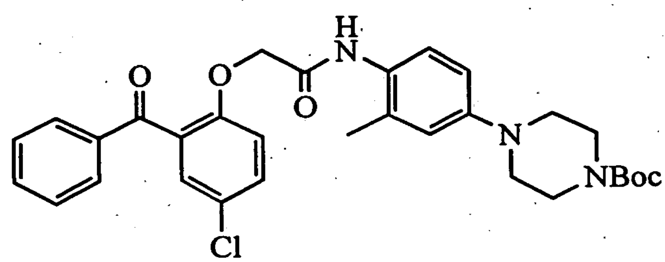
Step C:

Compound **364** (1.7 g, 8.9 mmol), NEt_3 (1.4 mL, 10 mmol), acetonitrile (12 mL), and acid chloride **320** (2.36 g, 7.6 mmol) in acetonitrile (12 mL) were used as in general procedure X. Water was added to the reaction mixture and the resulting suspension was filtered. The filtrate was partitioned between 2N NaOH and ethyl acetate. The aqueous layer was acidified with 1N sodium hydrogen sulfate to pH 1 and extracted with ethyl acetate. The product was purified by flash chromatography using a gradient between 3:2 hexanes:ethyl acetate, ethyl acetate, and methanol to afford **362** as a yellow solid (0.250 g) MS (ES^+) *m/z* 494 $(M+H)^+$ and **361** as an orange solid (0.005g, 0.1%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.96 (s, 3H), 2.79 (m, 4H), 2.97 (m, 4H), 4.66 (s, 2H), 6.66 (m, 2H), 7.05 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (t, 2H), 7.6 (t, 2H), 7.75 (d, 2H), 8.79 (s, 1H); MS (ES^+) *m/z* 464 $(M+H)^+$.

Example 152

The product was filtered through a celite pad eluted with 9:1 methylene chloride:methanol and concentrated in vacuo to afford **367** as a pink solid (2.926 g, crude material).

Step C:



368

Acid chloride **320** in methylene chloride was added dropwise to a solution of compound **367** (0.362 g, 1.24 mmol) in pyridine (20 mL) and stirred for 2 days. The reaction was concentrated in vacuo, ethanol and ice were added, and the resulting solid was filtered and washed with ether to afford **368** as a yellow solid (0.118 g, 20.2%). ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 1.38 (d, 9H), 1.95 (s, 3H), 3 (d, 4H), 3.4 (s, 4H), 4.67 (s, 2H), 6.7 (m, 2H), 7.1 (d, 1H), 7.42 (d, 1H), 7.48 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

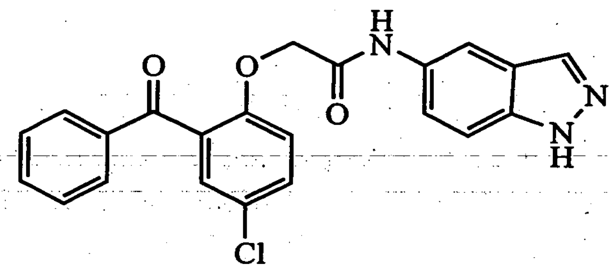
Step D:

TFA (15 mL, 195 mmol) was added to a solution of compound **368** (0.118 g, 0.21 mmol) in acetonitrile and stirred overnight. The reaction mixture was concentrated in vacuo after carbon tetrachloride was added to azeotrope off the TFA. This procedure was repeated multiple times. The mixture was concentrated in vacuo to afford **365** as a yellow solid (0.085 g, 88%). ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 1.96 (s, 3H), 3.08 (d, 4H), 3.17 (d, 4H), 4.67 (s, 2H), 6.72 (m, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (s, 1H), 7.46 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8 (bs, 1H), 8.86 (s, 1H); MS (ES$^+$) *m/z* 464 (M+H)$^+$.

<u>**Example 153**</u>

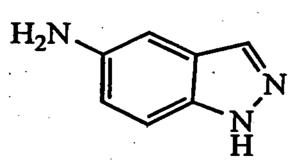
4-Nitroaniline (Sigma, 0.244 g, 1.77 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (5 mL), and acid chloride **320** (0.54 g, 1.75 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **371** as an off-white solid (0.012 g, 2%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.8 (s, 2H), 7.05 (d, 1H), 7.4 (d, 1H), 7.5 (m, 3H), 7.65 (t, 1H), 7.9 (d, 2H), 8 (d, 2H), 8.25 (d, 2H), 10 (s, 1H); MS (ES$^-$) *m/z* 409 (M-H)$^-$.

Example 155



372

Step A:



373

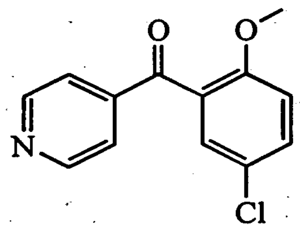
5-Nitroindazole (Aldrich, 1.2 g, 7.36 mmol), palladium on carbon (0.23 g, 10% w/w), ethanol (25 mL), and THF (5 mL) were used as in general procedure XII using 78 psi of hydrogen to afford **373** as a pink solid (0.98 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 6.7 (dd, 2H), 7.2 (D, 1H), 7.7 (S, 1H), 12.5 (S, 1H).

Step B:

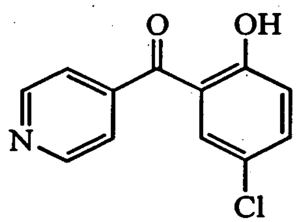
Compound **373** (1 g, 7 mmol), NEt_3 (1.2 mL, 8.6 mmol), acetonitrile (20 mL), and acid chloride **320** (1.9 g, 6.2 mmol) in acetonitrile (10 mL) were used as in general procedure X. Ice water was added and the resulting suspension was filtered, washed with water, and the solid was recrystallized from ethanol and water. The resulting precipitate was filtered

375

Compound **378** (0.143 g, 0.64 mmol) was added to a solution of compound **377** (0.15 g, 0.64 mmol), potassium carbonate (0.09 g, 0.65 mmol), and DMF (5 mL) and stirred overnight. The mixture was poured into ice water, filtered, and the resulting solid was washed with ether. The product was purified by TLC prep plate using 23:1 methylene chloride:methanol to afford **375** as an orange solid (0.021g, 9%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.06 (t, 1H), 7.25 (d, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.58 (s, 1H), 7.67 (m, 3H), 8.77 (d, 2H) 9.86 (s, 1H); MS (ES$^-$) *m/z* 366 (M-H)$^-$.

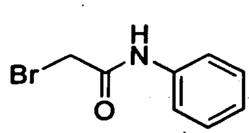


376



377

Compound **376** (4.2g, 17 mmol) in methylene chloride (100 mL), THF (100 mL), and BBr_3 (17g, 68 mmol) in methylene chloride (68 mL) were used as in general procedure IX to afford, after recrystallization from methanol, **377** as a yellow solid (1.1g, 28%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7 (d, 1H), 7.6 (d, 2H), 8.2 (d, 2H), 9.7 (bs, 2H), 10.95 (s, 1H); MS (ES$^-$) *m/z* 232 (M-H)$^-$.

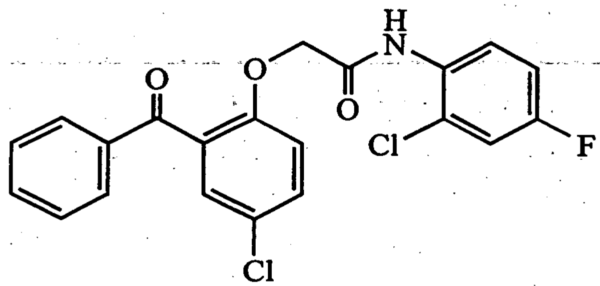


378

Example 158

%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.8 (s, 3H), 4.8 (s, 2H), 7.15 (d, 1H), 7.22 (d, 3H), 7.48 (m, 4H), 7.58 (d, 2H), 7.78 (d, 2H), 8.5 (s, 1H), 8.9 (s, 1H); MS (ES^{+}) *m/z* 575 $(M+H)^{+}$.

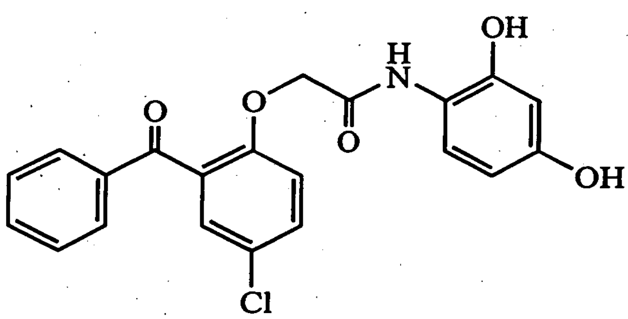
Example 160



381

Acid chloride **320** (0.68 g, 2.2 mmol) in methylene chloride (5 mL) was added to a solution of 2-chloro-4-fluoroaniline (Aldrich, 0.5 g, 3.4 mmol), pyridine (12 mL) and the mixture was stirred overnight. The reaction mixture was poured over ice, ethanol (30 mL) was added, and the precipitate was filtered and washed with 1:1 ethanol:water and diethyl ether to afford **381** as a white solid (0.367 g, 40%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8 (s, 2H), 7.25 (m, 2H), 7.5 (m, 9H), 7.65 (t, 2H), 7.75 (m, 1H), 7.8 (d, 2H), 9.2 (s, 1H); MS (ES^{+}) *m/z* 419 $(M+H)^{+}$.

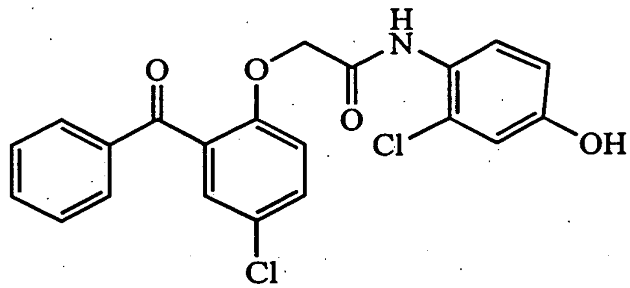
Example 161



382

Resorcinol hydrochloride (Aldrich, 0.5 g, 3.4 mmol), acetonitrile (20 mL total reaction volume), Et_3N (0.75 mL, 5.4 mmol), and acid chloride **320** (0.8 g, 2.6 mmol) in acetonitrile were used as in general procedure X. The reaction mixture was poured over ice water and ethanol was added to the solution. The mixture was recrystallized from

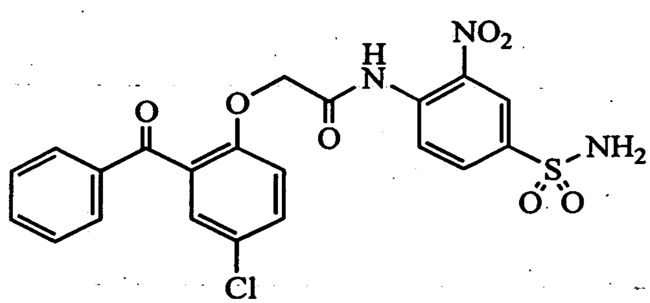
Example 163



385

Carboxylic acid **105** (0.29 g, 1 mmol), HCA (0.08 mL, 0.53 mmol), methylene chloride (5 mL total reaction volume), and PPh_3 (0.26 g, 1 mmol) were combined in a round-bottom flask under nitrogen at -78°C. 4-Amino-3-chlorophenol (Aldrich, 0.145 g, 1 mmol) was free-based by partitioning it between methylene chloride and saturated sodium bicarbonate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give a pink solid that was dissolved in methylene chloride and Et_3N (0.26 mL, 1.9 mmol) and added dropwise to the reaction mixture at -78°C. The reaction was warmed to rt and concentrated in vacuo. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **385** as an orange solid (0.120 g, 29%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 6.67 (d, 1H), 6.79 (s, 1H), 7.2 (d, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.9 (s, 1H), 9.8 (s, 1H); MS (ES^+) *m/z* 417 $(M+H)^+$.

Example 164

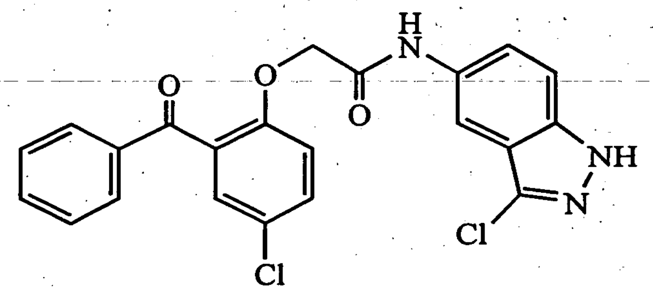


386

Carboxylic acid **105** (0.67 g, 2.3 mmol), HCA (0.17 mL, 1.1 mmol), THF, PPh_3 (0.61 g, 2.3 mmol) in THF, 2-nitro-4-sulfanilamide (0.5 g, 2.3 mmol) in THF (20 mL total reaction volume), and pyridine (2.25 mL, 28 mmol) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the product was purified by flash

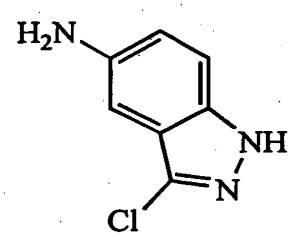
resulting solution was concentrated in vacuo. The concentrate was purified by flash chromatography using a gradient between 9:1 and 4:1 methylene chloride:methanol as elutant to give an oil. The oil was dissolved in methylene chloride and 1N HCl in Et_2O (3 mL) was added and the mixture was stored at rt for 7 d. The precipitate was filtered and washed with ether to afford **388** as a yellow orange solid (0.125 g, 10%). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.8 (m, 2H), 2.28 (s, 6H), 2.5 (m, 2), 4 (t, 2H), 4.8 (s, 2H), 6.9 (d, 1H), 7.08 (d, 1H), 7.25 (d, 1H), 7.45-7.58 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.05 (s, 1H); MS (ES^+) *m/z* 502 $(M+H)^+$.

Example 167



389

Step A:



390

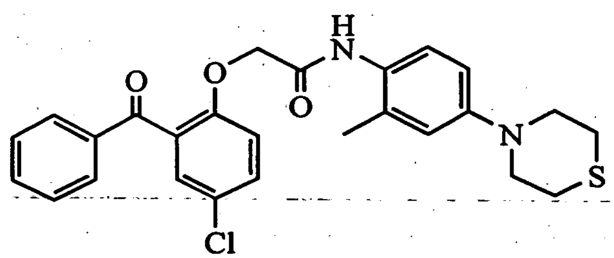
3-Chloro-5-nitroindazole (Lancaster, 5 g, 25 mmol), sodium dithionite (17.6 g, 101 mmol), ethanol (150 mL), and water (50 mL) were combined in a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand and then refluxed overnight. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in ethyl acetate, washed with brine and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give **390** as a yellow solid (1.3 g, 31%).

The reaction was cooled to rt and the resulting mixture was extracted with ethyl acetate. The organics were dried over $MgSO_4$ and concentrated in vacuo to give **392** as a white solid (0.394 g, 80%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.07 (s, 2H), 6.8 (d, 1H), 7 (s, 2H), 7.39 (dd, 1H), 7.55 (d, 1H); MS (ES$^-$) *m/z* 205 (M-H)$^-$.

Step B:

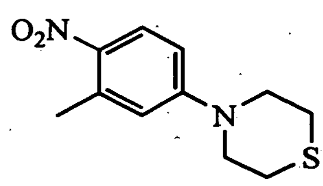
Carboxylic acid **105** (0.54 g, 1.9 mmol), HCA (0.14 mL, 0.92 mmol), THF, PPh_3 (0.49 g, 1.9 mmol) in THF, compound **392** (0.384 g, 1.9 mmol), in THF (40 mL total reaction volume), and pyridine (1.8 mL) were used as in general procedure XIII. The reaction mixture was concentrated and the resulting solid was dissolved in ethanol. Water was added and the precipitate was filtered and washed with 1:1 ethanol:water and ether to afford **391** as a white solid (0.206 g, 23.1%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.8 (s, 2H), 7.2 (d, 1H), 7.43 (s, 2H), 7.47 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 3H), 7.8 (d, 1H), 8.05 (d, 1H), 9.3 (s, 1H).

<u>**Example 169**</u>



393

Step A:

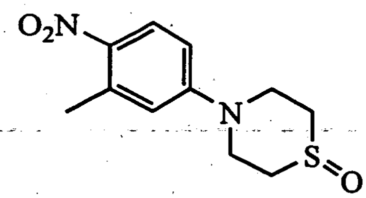


394

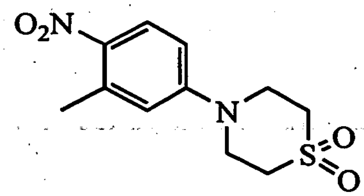
5-Fluoro-2-nitrotoluene (Aldrich, 50.6 g, 364 mmol), DMSO (60 mL), and thiomorpholine (37 mL, 368 mmol) were combined and heated to 75°C for 2 h and 100°C for 4h under nitrogen. The reaction was cooled to rt. Ether was added to the mixture and the slurry was stirred vigorously. Water was added to the slurry and the resulting solid was filtered

396

Step A:



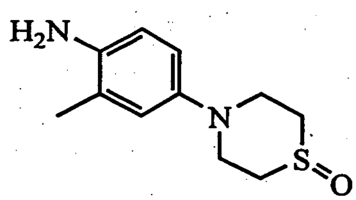
397



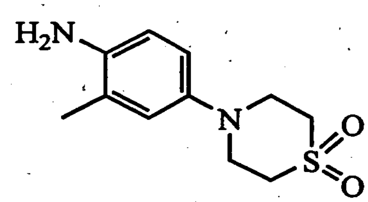
398

3-chloroperoxybenzoic acid (Aldrich, 0.046 g, 2.7 mmol) in methylene chloride was added dropwise to a stirred solution of compound **394** (12.5 g, 52.4 mmol) in methylene chloride (300 mL total volume for reaction) at -20 °C and the mixture was stirred for 1.5 h after which the cooling bath was removed and the reaction was stirred at rt overnight under nitrogen. The mixture was washed with saturated sodium metabisulfite, 2N NaOH, and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of **397** and **398** as a yellow solid (12.2 g, crude mixture).

Step B:



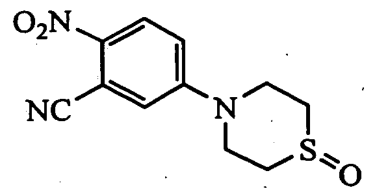
399



400

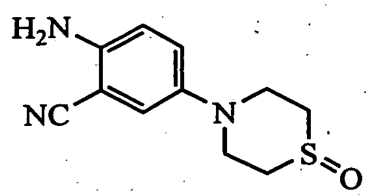
The mixture of **397** and **398** (12.3 g), palladium on carbon (3.7 g, 10% w/w), ethanol (100 mL), THF (30 mL), and methanol (75 mL) were used as in general procedure XII using 60 psi of hydrogen to afford an oil. The product was purified on silica gel by flash chromatography using 7:3 hexanes:ethyl acetate, 100% ethyl acetate, and 4:1 ethyl acetate:methanol as elutants to afford **399** as an orange solid (4.27 g, 39%) ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 2.68 (d, 2H), 2.87 (t, 2H), 3.15 (dd, 2H), 3.44 (t, 2H), 4.38 (bs, 2H), 6.49 (d, 1H), 6.59 (d, 1H), 6.64 (s, 1H); MS (ES$^+$) *m/z* 225 $(M+H)^+$ and **400** as a tan solid (3.57 g, 31%) ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 3.08 (m,

Step B:



403

3-Chloroperoxybenzoic acid (Aldrich, 4.85 g, 17 mmol) in methylene chloride was added to a cooled solution of compound **402** (3 g, 12 mmol) in methylene chloride (100 mL total volume for reaction) at -20°C and the mixture was stirred for 15 min. after which the cooling bath was removed and the mixture was stirred at rt for 4 h under nitrogen. The reaction mixture was washed with saturated sodium metabisulfite, 2N NaOH, and brine. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford **403** as a yellow solid (0.59 g, crude material). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.63 (m, 4H), 3.9 (m, 4H), 7.2 (dd, 1H), 7.5 (d, 1H), 8.1 (d, 1H).



404

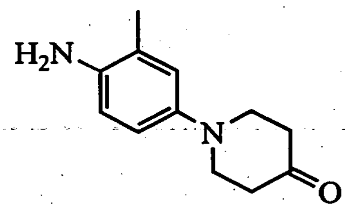
Palladium on carbon (0.23 g, 10% w/w), compound **403** (0.5 g, 1.9 mmol), ethanol (30 mL total reaction volume), THF (20 mL), and methanol (20 mL) were used as in general procedure XII to afford **404** as a green oil (0.41 g, 93%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.68 (d, 2H), 2.9 (t, 2H), 3.3 (d, 2H), 3.55 (t, 2H), 5.6 (bs, 2H), 6.79 (d, 1H), 7.02 (d, 1H), 7.17 (dd, 1H).

Step C:

Compound **404** (0.41 g, 1.8 mmol), HCA (0.132 mL, 0.87 mmol), PPh_3 (0.46 g, 1.75 mmol), pyridine (1.7 mL, 21 mmol), THF (25 mL), and carboxylic acid **105** (0.51 g, 1.8 mmol) were used as in general procedure XIII. The concentrate was purified by flash

PU3517

Step B:

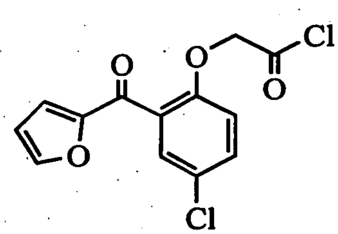


407

Compound **406** (0.57 g, 2.4 mmol), palladium on carbon (0.17 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 70 psi hydrogen to afford **407** as a yellow oil (0.5 g, crude material).

Step C:

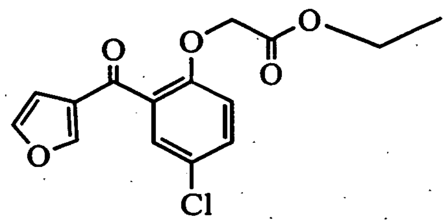
Compound **407** (0.5 g, 2.1 mmol), HCA (0.16 mL, 1.05 mmol), PPh_3 (0.56 g, 2.1 mmol), pyridine (2 mL, 25 mmol), THF (50 mL), and carboxylic acid **105** (0.62 g, 2.1 mmol) were used as in general procedure XIII. The mixture was concentrated in vacuo and purified on by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and 100% ethyl acetate as elutant to afford **405** as a yellow solid (0.32 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2 (s, 3H), 2.4 (m, 4H), 3.58 (m, 4H), 4.7 (s, 2H), 6.85 (d, 1H), 6.9 (s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.48 (s, 1H), 7.55 (t, 2H), 7.65 (t, 2H), 7.8 (d, 2H), 8.85 (s, 1H); MS (ES$^+$) *m/z* 478 (M+H)$^+$.



408

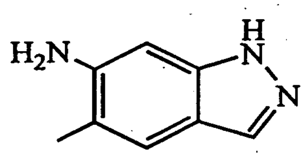
Carboxylic acid **115** (1 g, 3.6 mmol), methylene chloride (30 mL), and thionyl chloride (7.6 mL, 104 mmol) were used as in general procedure XV to afford **408** as a purple oil (1.24 g, crude material).

(DMSO-d_6, 400 MHz) δ 6.8 (s, 1H), 6.95 (d, 1H), 7.4 (m, 2H), 7.8 (s, 1H), 8.25 (s, 1H), 10.45 (s, 1H).



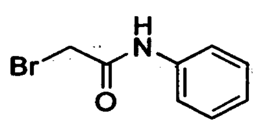
412

Phenol **411** (12.3 g, 55.3 mmol), potassium carbonate (38.21 g, 277 mmol), ethyl bromoacetate (6.4 mL, 57.7 mmol), and acetone (250 mL) were used as in general procedure II to afford **412** as a yellow/orange foam (15.9 g, 93%). MS (ES$^-$) *m/z* 279 (M-H)$^-$. The crude product was used without purification.



413

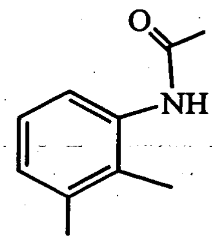
Compound **415** (0.4 g, 2.3 mmol), palladium on carbon (0.12 g, 10% w/w), and ethanol (50 mL) were used as in general procedure XII using 60 psi of hydrogen to afford **413** as a tan solid (0.35 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (s, 3H), 4.96 (bs, 2H), 6.56 (s, 1H), 7.22 (s, 1H), 7.63 (s, 1H), 12.16 (s, 1H); MS (ES$^-$) *m/z* 148 (M-H)$^-$.



414

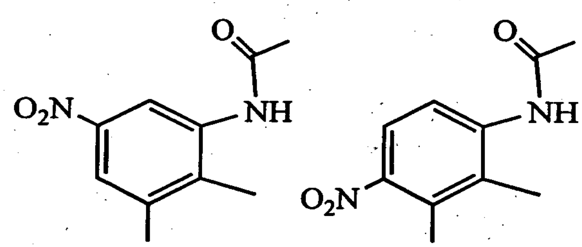
Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,4-dimethylaniline (Aldrich, 4.94 g, 40.8 mmol) at 0 °C. The reaction was stirred for 3 h. The mixture was poured into ice water (1800 mL) and extracted with ethyl acetate. The organics were separated and concentrated in vacuo to afford **414** as an orange solid (2.98

3H), 4.5 (s, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.85 (s, 1H), 12.55 (bs, 1H). MS (ES$^-$) *m/z* 148 (M-H)$^-$.



417

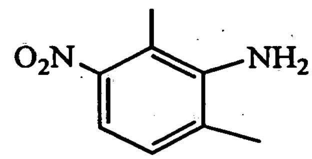
Acetic anhydride (25 mL, 265 mmol) was added to a stirred solution of 2,3-dimethylaniline (Aldrich, 31.2 g, 257 mmol) and toluene (50 mL) under nitrogen. The resulting solid was filtered and washed with hexanes and ether to afford **417** as a white solid (40.59 g, crude material). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.06 (d, 6H), 2.26 (s, 3H), 7.05 (m, 2H), 7.15 (d, 1H), 9.35 (bs, 1H).



418

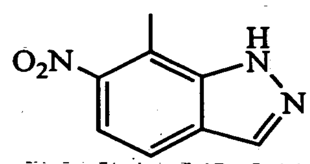
Potassium nitrate (6.2 g, 61 mmol) in concentrated sulfuric acid (75 mL) was added dropwise over 1 h to a cooled, stirred solution of concentrated sulfuric acid (50 mL) and compound **417** (10 g, 61 mmol) at -17 °C. The cooling bath was removed and the reaction was stirred at 0 °C for 1 h. The solution was poured into ice water (2000 mL) and stirred vigorously. The solution was extracted with methylene chloride. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford a solid. The solid was purified by flash chromatography using a gradient between 7:3 hexanes:ethyl acetate and ethyl acetate as elutant to afford **418** as a yellow solid (4.24g, 33%). MS (ES$^-$) *m/z* 201 (M-H)$^-$. Compound **418** was used as a mixture without purification.

afford **421** as a tan solid (1.43 g, 63.8%). The crude material was used without purification.



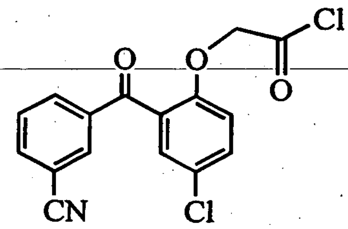
422

Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,6-dimethylaniline (Aldrich, 12.32 g, 100 mmol) at -10 °C and stirred for 1 h. The mixture was poured into ice water and extracted with ethyl acetate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford **422** as an orange solid (5.63 g, 34%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (d, 6H), 5.4 (bs, 2H), 6.9 (d, 1H), 6.96 (d, 2H). The crude material was used without purification.



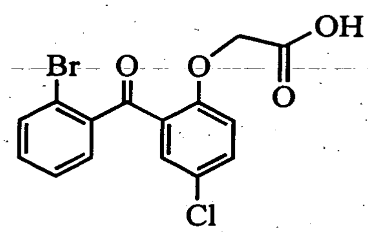
423

Sodium nitrite (2.34 g, 34 mmol) in water (10 mL) was added dropwise to a stirred solution of compound **422** (5.63 g, 34 mmol) and glacial acetic acid (500 mL) at 0°C and stirred for 15 min. The cooling bath was removed and the reaction was stored at rt for 6 d. The mixture was concentrated in vacuo and the concentrate was triturated with water. The resulting solid was filtered and recrystallized from methanol to give **423** as a red solid (2.69 g, 45%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.73 (s, 3H), 3.15 (s, 3H), 7.64 (d, 1H), 7.9 (d, 1H), 8.24 (s, 1H), 13.85 (bs, 1H). MS (ES$^-$) *m/z* 176 (M-H)$^-$. The crude material was used without purification.



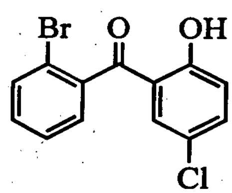
427

Carboxylic acid **129** (1.5 g, 4.8 mmol), methylene chloride (30 mL), and thionyl chloride(10 mL, 137 mmol) were used as in general procedure XV to afford **427** as an off-white, sticky solid (1.58 g, crude material).



428

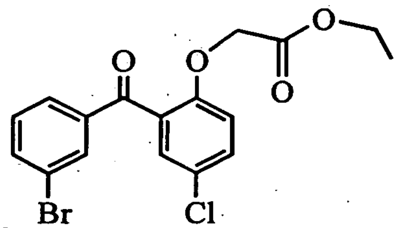
Ester **430** (17.24 g, 43 mmol), ethanol (200 mL), water (50 mL), and lithium hydroxide monohydrate (2.27 g, 54 mmol) were used as in general procedure III to afford **123** as a white solid (6.53 g, 41%).



429

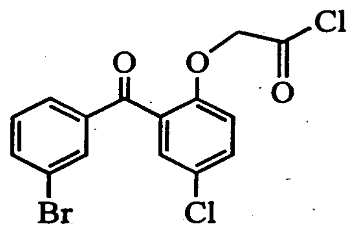
2-Bromobenzoyl chloride (10 g, 46 mmol), aluminum chloride ($AlCl_3$, 6.2 g, 46 mmol), CH_2Cl_2 (250 mL), and 4-chloroanisole (5.6 mL, 46 mmol) were used as in general procedure I to afford **429** as a tan solid (13.76 g, crude material).

general procedure I to afford, after triturating the concentrate with hexanes and filtering, **432** as a green solid (25.57 g, 75%). The crude material was used without purification.



433

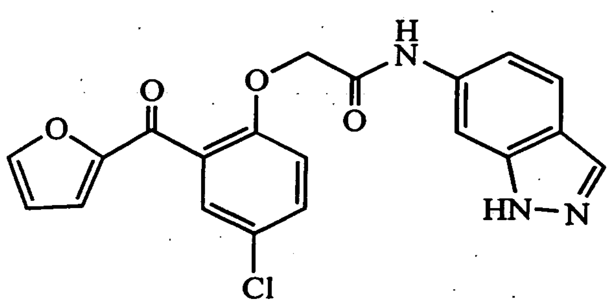
Compound **432** (9.08 g, 29 mmol), potassium carbonate (20.14 g, 146 mmol), ethyl bromoacetate (3.39 mL, 31 mmol), and acetone (200 mL) were used as in general procedure II to afford **433** as a red/brown oil (12.68 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.12 (t, 3H), 4.06 (q, 2H), 4.75 (s, 2H), 7.11 (d, 1H), 7.44 (t, 2H), 7.54 (d, 1H), 7.69 (d, 1H), 7.83 (d, 2H); MS (ES$^+$) *m/z* 398 (M+H)$^+$.



434

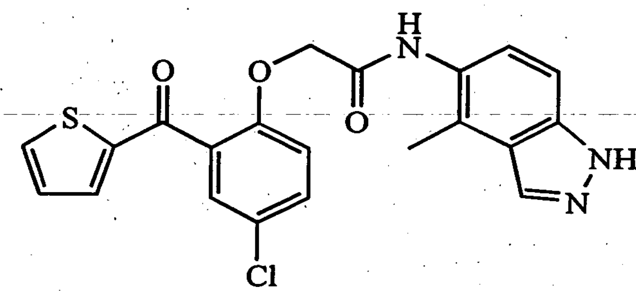
Carboxylic acid **431** (3 g, 8.1 mmol), methylene chloride (25 mL), and thionyl chloride(11.84 mL, 162 mmol) were used as in general procedure XV to afford **434** as a light brown oil (2.96 g, 94%). The crude material was used without purification.

Example 173



Compound **416** (0.1 g, 0.68 mmol), NEt_3 (0.14 mL, 0.71 mmol), acetonitrile (5 mL total reaction volume), and acid chloride **1** (0.53 g, 1.7 mmol) in acetonitrile were used as in general procedure X. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate to afford **437** as an off-white solid (0.095 g, 33%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.28 (s, 3H), 4.78 (s, 2H), 7.15 (d, 1H), 7.3 (t, 2H), 7.55 (dd, 3H), 7.65 (t, 2H), 7.82 (d, 2H), 8.13 (s, 1H), 9.18 (s, 1H), 13.04 (bs, 1H); MS (ES$^+$) *m/z* 420 (M+H)$^+$.

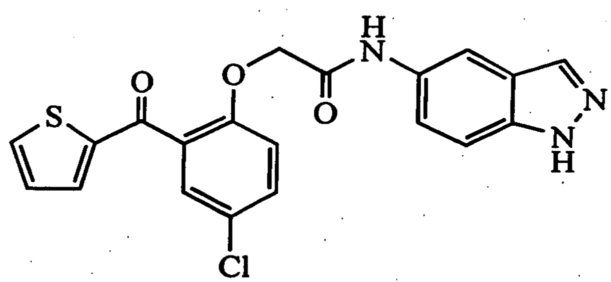
Example 176



438

Compound **112** (0.20g, 0.67 mmol), HOBt (0.09 g, 0.68 mmol), DMF (2 mL), compound **416** (0.1 g, 0.68 mmol) in DMF (3 mL), EDAC (0.13 g, 0.69 mmol), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 7:3 ethyl acetate:hexanes and 100% ethyl acetate to afford **438** as an off-white solid (0.192 g, 67%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.3 (s, 3H), 4.85 (s, 2H), 7.2-7.35 (m, 4H), 7.55 (s, 1H), 7.65 (d, 1H), 7.7 (s, 1H), 8.15 (s, 2H), 9.38 (s, 1H), 13.05 (s, 1H); MS (ES$^-$) *m/z* 424 (M-H)$^-$.

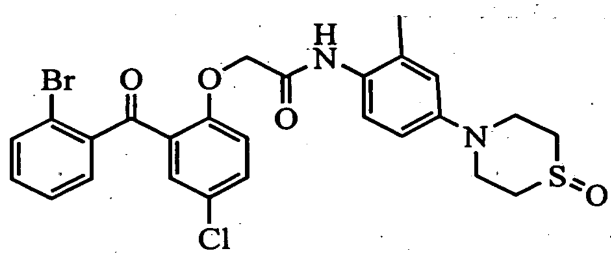
Example 177



439

Compound **399** (1.2 g, 5.4 mmol) in acetonitrile (45 mL total reaction volume),acid chloride **427** (1.22 g, 3.65 mmol) in acetonitrile, and NEt_3 (0.71 mL, 5.1 mmol) were used as in general procedure X. The product was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant to afford **441** as an off-white solid (0.59 g, 31%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.97 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.67 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.06 (d, 1H), 7.2 (d, 1H), 7.48 (s, 1H), 7.65 (t, 2H), 8.05 (bs, 2H), 8.15 (s, 1H), 8.96 (s, 1H).

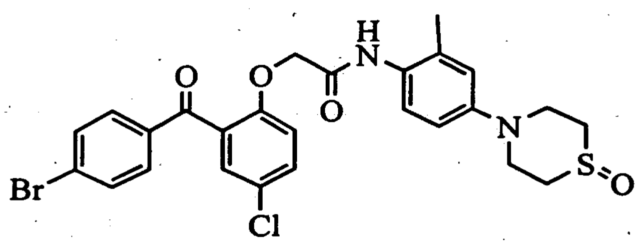
Example 180



442

Compound **428** (0.443 g, 1.2 mmol), HOBt (0.16 g, 1.2 mmol), DMF, compound **399** (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and Et_3N (0.34 mL, 2.4 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **442** as an off-white foam (0.154 g, 22%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.62 (s, 2H), 6.78 (d, 1H), 6.84 (s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.38 (t, 1H), 7.42 (d, 2H), 7.5 (t, 1H), 7.65 (m, 2H), 8.8 (s, 1H).

Example 181



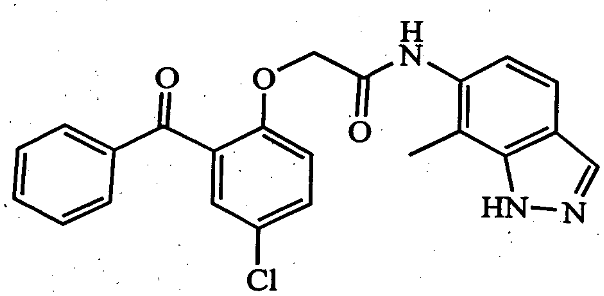
443

Compound **424** (0.443 g, 1.2 mmol), HOBt (0.16 g, 1.2 mmol), DMF, compound **399** (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and

445

Copper cyanide (0.037 g, 0.42 mmol) was added to a solution of compound **442** (0.120 g, 0.21 mmol) in DMSO (5 mL) and the reaction was heated to 160 °C and stirred overnight. The mixture was cooled and water was added to it. The resulting solid was filtered and washed with ethyl acetate. The filtrate was separated, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate as the elutant to afford **445** as an orange foam (0.012 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 2.62 (d, 2H), 2.86 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.62 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.05 (d, 1H), 7.2 (d, 1H), 7.55 (d, 1H), 7.7 (m, 4H), 7.98 (d, 1H), 8.97 (s, 1H); MS (ES$^-$) *m/z* 521 (M-H)$^-$.

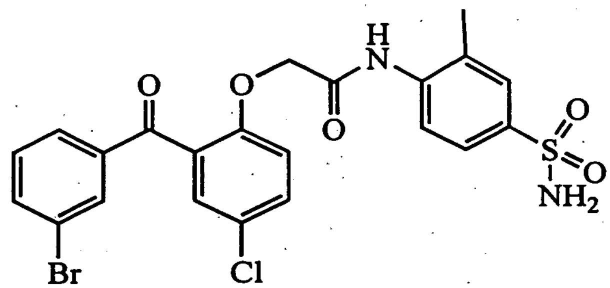
<u>**Example 184**</u>



446

Carboxylic acid **105** (0.296 g, 1.2 mmol), HOBt (0.136 g, 1.02 mmol), DMF, compound **421** (0.296 g, 1.02 mmol) in DMF (10 mL total reaction volume), EDAC (0.193 g, 1.02 mmol), and Et_3N (0.284 mL, 2.04 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 1:1 ethyl acetate:hexanes as elutant. The concentrate was dissolved in methylene chloride, washed with 10% potassium carbonate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was triturated with ethyl acetate and filtered to afford **446** as an off-white solid (0.0081 g, 2%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.2 (s, 3H), 4.74 (s, 2H), 6.95 (d, 1H), 7.22 (d, 1H), 7.45 (m, 4H), 7.6 (m, 2H), 7.75 (d, 2H), 7.98 (s, 1H), 9.25 (s, 1H) 13.05 (bs, 1H); MS (ES$^+$) *m/z* 420 (M+H)$^+$.

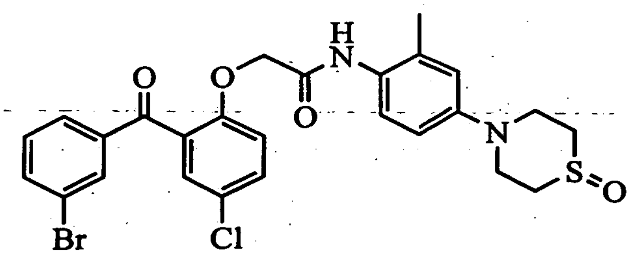
Example 187



449

Compound **466** (0.141 g, 0.757 mmol), NEt_3 (0.106 mL, 0.761 mmol), acetonitrile (20 mL total reaction volume), and acid chloride **434** (0.203 g, 0.523 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **449** as an off-white solid (0.038 g, 14%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.14 (s, 3H), 4.77 (s, 2H), 7.22 (m, 3H), 7.45 (dd, 2H), 7.6 (m, 4H), 7.72 (d, 1H), 7.82 (d, 1H), 7.88 (s, 1H), 9.3 (s, 1H); MS (ES$^-$) *m/z* 536 (M-H)$^-$.

Example 188

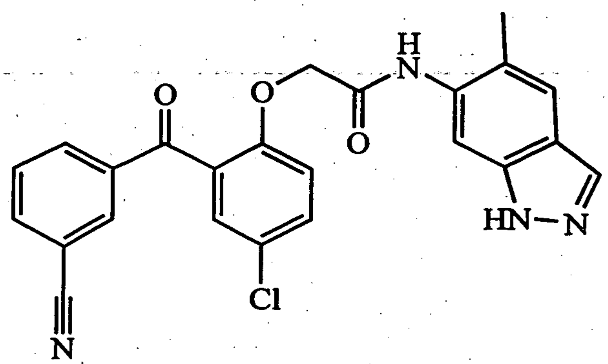


450

Compound **399** (1.43 g, 6.37 mmol), NEt_3 (0.888 mL, 6.37 mmol), acetonitrile (50 mL total reaction volume), and acid chloride **434** (1.68 g, 4.64 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **450** as an beige solid (1.3 g, 52%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (s, 3H), 2.62 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.82 (d, 1H), 7.08 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (d, 1H), 7.62 (dd, 1H), 7.7 (d, 1H), 7.81 (d, 1H), 7.88 (s, 1H), 8.9 (s, 1H); MS (ES$^-$) *m/z* 574 (M-H)$^-$.

4H), 4,74 (s, 2H), 6.72 (d, 2H), 6.77 (s, 1H), 7.19 (t, 2H), 7.3 (d, 1H), 7.5 (d, 3H), 7.57 (dd, 1H), 8.05 (s, 1H), 9.01 (s, 1H); MS (ES$^-$) *m/z* 553 (M-H)$^-$.

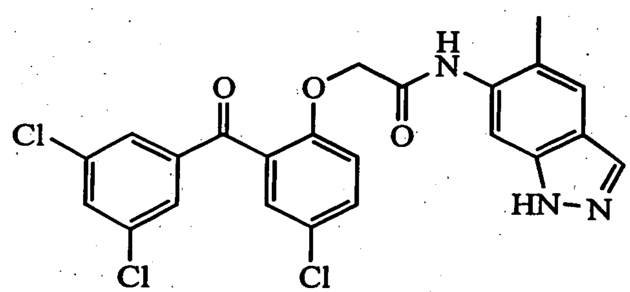
Example 191



453

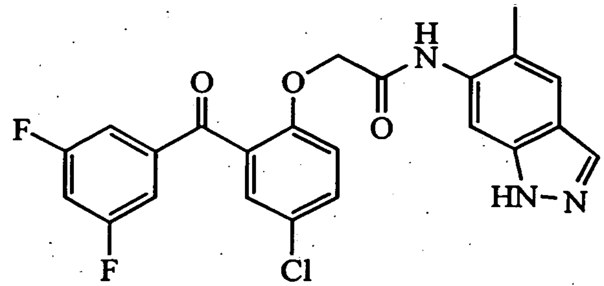
Compound **413** (0.072 g, 0.49 mmol) in acetonitrile (10 mL total reaction volume), acid chloride **427** (0.163 g, 0.49 mmol) in acetonitrile, and NEt_3 (0.1 mL, 0.72 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **453** as an off-white solid (0.013 g, 6%). ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 2.16 (s, 3H), 4.77 (s, 2H), 7.25 (d, 1H), 7.5 (s, 2H), 7.65 (m, 3H), 7.89 (s, 1H), 8.08 (d, 2H), 8.16 (s, 1H), 9.03 (s, 1H), 12.84 (s, 1H); MS (ES$^-$) *m/z* 443 (M-H)$^-$.

Example 192



454

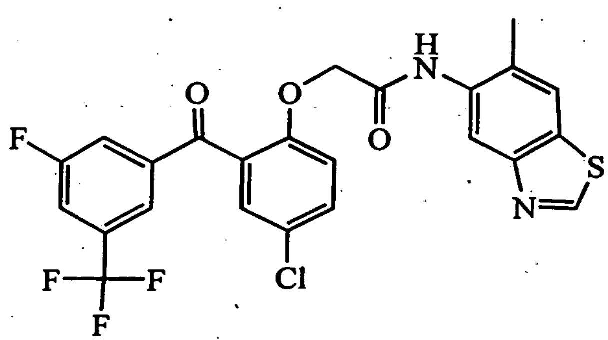
Carboxylic acid **76** (0.2 g, 0.55 mmol), methylene chloride (CH_2Cl_2, 3 mL), DMF (4 drops), oxalyl chloride (0.13 mL, 1.49 mmol) were used as in general procedure V. The resulting acid chloride was added to a solution of the amine **413** (0.081 g, 0.55 mmol), acetone (5 mL), sodium bicarbonate (0.42 g, 5 mmol), and water (0.5 mL) as used in



456

Carboxylic acid **49** (0.2 g, 0.6 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.16 mL, 1.8 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **413** (0.09 g, 0.61 mmol), acetone (10 mL), sodium bicarbonate (0.453 g, 5.4 mmol), and water (0.5 mL) as used in general procedure VI. The reaction mixture was heated to 40 °C for 1 h, after which time water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to give a gray solid. The product was purified by filtering through a silica gel plug eluded with 9:1 hexanes:ethyl acetate. Hexanes were added to the filtrate until a solid formed. The solid was filtered to afford **456** as a white solid (0.034 g, 12%). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.2 (s, 3H), 4.85 (s, 2H), 7.3 (d, 1H), 7.5 (d, 2H), 7.56 (d, 2H), 7.62(d, 1H), 7.7 (d, 1H), 7.77 (s, 1H), 7.95 (s, 1H), 9.19 (s, 1H), 12.9 (s, 1H); MS (ES$^-$) *m/z* 454 (M-H)$^-$.

Example 195

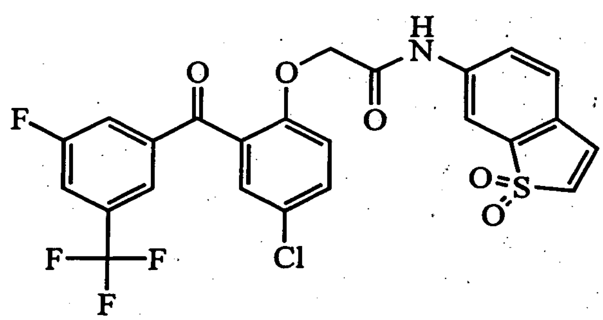


to give an oil. The product was purified by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and ethyl acetate as elutant to afford **460** as a white solid (0.03g, 8%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 5.09 (bs, 2H), 7.28 (s, 1H), 7.66 (s, 1H), 9.1 (s, 1H); MS (ES$^+$) *m/z* 165 (M+H)$^+$.

Step D:

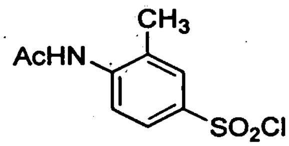
Carboxylic acid **71** (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **460** (0.03 g, 0.18 mmol), acetone (5 mL), sodium bicarbonate (0.18 g, 2.1 mmol), and water (0.5 mL) as used in general procedure VI. The mixture was filtered and the solids were washed with water, ether, and ethyl acetate to afford **457** as an off-white solid (0.064 g, 67%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.18 (s, 3H), 4.79 (s, 2H), 7.25 (d, 1H), 7.54 (d, 1H), 7.65 (dd, 1H), 7.88 (d, 2H), 7.95 (s, 1H), 7.98 (d, 1H), 8.06 (s, 1H), 9.27 (s, 1H), 9.38 (bs, 1H); MS (ES$^-$) *m/z* 521 (M-H)$^-$.

Example 196



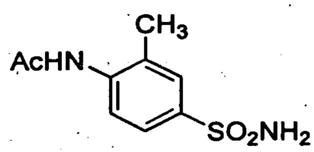
461

Carboxylic acid **71** (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V and added to a solution of 6-amino-1,1-dioxobenzo(b)thiophene (Maybridge, 0.044 g, 0.24 mmol), acetone (10 mL), sodium bicarbonate (0.184 g, 2.2 mmol), and water (1 mL) as used in general procedure VI. The product was purified by filtering through a silica pad eluted with methylene chloride. The organics were washed with saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated in vacuo. The product was further purified by flash



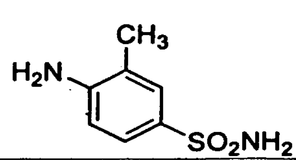
464

Sulfonic acid salt **463** (42.34 g, 169 mmol) and DMF (300 mL) were added to a flask that was equipped with a stir bar and nitrogen on demand and was cooled to 0 °C. Thionyl chloride (30 mL, 411 mmol) was added dropwise from an addition funnel at a rate such that the temperature of the reaction mixture did not exceed 10 °C. When the addition was complete, the mixture was allowed to warm to rt and stir for an additional 2 1/2 h, after which time it was poured into a beaker containing crushed ice. The resulting solid was collected by filtration, washed with several portions of water and dried under vacuum (25.63 g, 61%). ^{1}H NMR (DMSO, d_6, 400 MHz) δ 2.02 (s, 3H), 2.15 (s, 3H), 7.33 (s, 2H), 7.38 (s, 1H), 9.27 (s, 1H).



465

Into a round-bottom flask, equipped with a stir bar and nitrogen on demand, were placed sodium acetate (19.82 g, 241.6 mmol) and ethyl alcohol (200 mL) and the mixture was cooled to 0 °C. Ammonia gas was bubbled through the sodium acetate solution for 5 min, then sulfonyl chloride **464** (25.63 g, 103 mmol) was added as a solid and in one portion. The resulting mixture was allowed to stir at 0 °C for 30 min, and was then allowed to warm to rt and stir for an additional 18 h. The mixture was then diluted with water and was poured into a separatory funnel containing water and ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **465** as a yellow solid (8.4 g, 36%), which was used without further purification.



HeLa-CD4-LTR-β-gal cells were obtained from the NIH AIDS Research and Reference Reagent Program. Cells were propagated in DMEM containing 10% fetal bovine serum, 0.2 mg/ml geneticin and 0.1 mg/ml hygromycin B. Cells were routinely split by trypsinization when confluency reached 80% (approximately every 2 to 3 days).

B. Construction of HIV-1 reverse transcriptase (RT) mutants

DNA encoding the HIV-1 reverse transcriptase was subcloned from a M13 phage into a general shuttle vector, pBCSK+, as a ~1.65 kbp EcoRI/HindIII ended DNA fragment. The HIV DNA insert of the resulting plasmid, pRT2, was completely sequenced on both strands prior to use in site directed mutagenesis experiments. Specific amino acid replacements were made using Stratagene Quick Change reagents and mutagenic oligonucleotides from Oligos. Following mutagenesis, the entire mutant RT coding sequence was verified by sequencing both DNA strands.

C. Construction of isogenic HIV-1 RT mutant virus

Mutant HIV-1 strains were isolated by a modified Recombinant Virus Assay (Kellam P. and Larder B., Recombinant virus assay: a rapid, phenotypic assay for assessment of drug susceptibility of human immunodeficiency virus type 1 isolates,38:23-30, 1994). 1 X 10^7 Jurkat T-cells (maintained in RPMI containing 10% fetal bovine serum, split 1:5 every 5 to 6 days) were co-transfected with EcoRI/HindIII digested mutant RT plasmid and Bst EII-digested HIV-$1_{HXB2\Delta RT}$ DNA in the presence of DMRIE-C transfection reagent (Gibco) according to supplier's recommended protocol. Each mutant RT coding sequence was crossed into the RT-deleted HIV-1 viral DNA backbone by in vivo homologous recombination. Transfected cell cultures were expanded and monitored until syncitia formation and CPE were extensive. Virus was harvested by clear spin of the culture supernatants and frozen at - 80 C as primary stock. Recombinant progeny virus was sequenced in the RT region to confirm the mutant genotype. Virus stocks were further expanded by infection of Jurkat cells, harvested and stored as frozen aliquots. Stocks were titered in HeLa MAGI cells for assay.

D. Titering of virus stocks

Following incubation, the chemiluminescence of each well was measured with a Dynatech plate reader using the following settings:

PARAMETER	VALUE
run	cycle
data	all
gain	low
cycles	1s
pause	2s
rows	abcdefgh
temp	room
stir	off

The output raw data, RLUs, were analyzed by nonlinear regression to determine IC_{50} values (see data analysis section below).

F. Data Analysis

Relative light units (RLU) are expressed as % control:

$$(\text{RLU at compound [ ] / RLU no compound})*100 = \%\ \text{Control}$$

The concentration of compound that inhibits 50% of the signal produced in untreated samples (IC_{50}) is determined by the following nonlinear regression model available on the ROBOSAGE software package:

$$Y = V_{max}*(1-(X^n/(K^n + X^n)))$$

This equation describes a sigmoidal inhibition curve with a zero baseline. X is inhibitor concentration and Y is the response being inhibited. V_{max} is the limiting response as X approaches zero. As X increases without bound, Y tends toward its lower limit, zero. K is the IC_{50} for the inhibition curve, that is, Y is equal to 50% of V_{max} when X = K.

Results in Table 1 are reported as ranges of representative IC_{50} values.

II. MT4 Cell Assay

A. Experimental Procedure

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in

Percent of cells remaining = (compound-treated uninfected cells, rfU / untreated uninfected cells) x 100.

A level of percent of cells remaining of 79% or less indicates a significant level of direct compound-induced cytotoxicity for the compound at that concentration. When this condition occurs the results from the compound-treated infected wells at this concentration are not included in the calculation of IC_{50}.

For measurements of compound antiviral activity, results from wells containing various compound concentrations and infected cells are compared to the average of uninfected and infected cells without compound treatment. Percent inhibition of virus is determined by the following formula:

Percent inhibition of virus = (1-((ave. untreated uninfected cells - treated infected cells) / (ave. untreated uninfected cells - ave. untreated infected cells)))x 100

References:

1. Averett, D.R., Anti-HIV compound assessment by two novel high capacity assays, *J. Virol. Methods* 23: 263-276, 1989.

2. Schwartz, O., et al,. A rapid and simple colorimetric test for the study of anti-HIV agents, *AIDS Res. and Human Retroviruses* 4 (6): 441-447, 1988..

3. Daluge, S.M., et al., 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immunodeficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother.* 38 (7): 1590-1603, 1994.

4. Dornsife, R.E., et al., Anti-human immunodeficiency virus synergism by zidovudine (3'-azidothymidine) and didanosine (dideoxyinosine) contrasts with the additive inhibition of normal human marrow progenitor cells, *Antimicro. Agents and Chemother.* 35 (2): 322-328, 1991.

Results in Table 1. are expressed as representative IC_{50} ranges.

Table 1

Compound Number	Virus Type	IC50 (nM) Range *	Assay
1	HIV-1	C	MT4
	NEV-R	D	MT4

79	HIV-1	A	MT4
	HIV-2	D	MT4
	NEV-R	A	MT4
	K103N	A	HeLa
	K103N/Y181C	A	HeLa
103	HIV-1	B	MT4
	NEV-R	C	MT4
	K103N	B	HeLa
120	HIV-1	B	MT4
	NEV-R	B	MT4
	K103N	B	HeLa
	K103N/Y181C	C	HeLa
	WTRVA	B	HeLa
	Y181C	B	HeLa
122	HIV-1	A	MT4
	NEV-R	B	MT4
	K103N	B	HeLa
	K103N/Y181C	D	HeLa
	WTRVA	B	HeLa
	Y181C	C	HeLa
239	HIV-1	A	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L100I	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V108I	A	HeLa
	K103N/Y181C	B	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A	B	HeLa
	V106A/Y181C	C	HeLa
	V106I	A	HeLa
	V106I/Y181C	A	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
257	HIV-1	A	MT4
	NEV-R	A	MT4

	K103N/Y181C	B	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	B	HeLa
	V106A	B	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
453	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	B	HeLa
	V106A	C	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	C	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa

* A indicates an IC_{50} of 10nM or less
B indicates an IC_{50} between 11nM and 100nM
C indicates an IC_{50} between 101nM and 1,000nM
D indicates an IC_{50} between 1,000nM and 3,000nM

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy;
or a pharmaceutically acceptable derivative thereof.

2. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally subsituted with one or more subsitutents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted withhalogen; R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy; $-NH_2$; or heterocycle; R^2 is hydrogen; R^3 is hydrogen or C_{1-8} alkyl; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more

$-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $-C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$;

R^{10} is C_{1-8}alkyl;

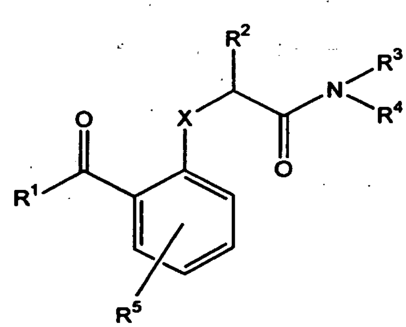
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2$, $-S(O)_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

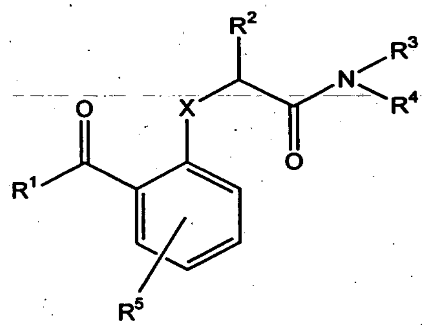
7. A compound of formula (IB) according to claim 6 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, and -CN; R^2 is hydrogen; R^3 is hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

8. A compound of formula (IC):



9. A compound of formula (IC) according to claim 8 wherein X is O; R^1 is heterocycle, optionally substituted with -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-OR^{11}$, and heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo; R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

10. A compound of formula (ID):



(ID)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally subsituted with one or more subsitutents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, and $-SR^{10}N(R^{10})_2$; or R^3 and R^4 together with the nitrogen atom to which they are attached form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen; halogen; or C_{1-8}alkyl;

R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$;

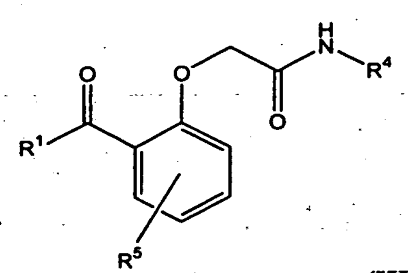
provided that when X is O, and R^1 is unsubstituted C_{6-14}aryl, then R^3R^4 is substituted.

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

14. A compound of formula (II) according to claim 13 wherein R^1 is C_{6-14}aryl which is substituted with halogen; R^2 is hydrogen; R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

15. A compound of formula (III):



(III)

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2$, $-S(O)_2NR^8R^9$, $-NR^8R^9$ and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof,
provided that:
(a) when R^3 is H and R^4 is C_{6-14}aryl substituted with OR^{11} wherein R^{11} is NR^8R^9 wherein R^8 and R^9 are C_{1-8}alkyl, and R^1 is C_{6-14}aryl, then R^1 cannot be substituted in the para position, and
(b) when R^3 is H and R^4 is unsubsituted C_{6-14}aryl, then R^1 cannot be 3-pyridyl or cyclopentyl, and
(c) R^1 and R^4 cannot both be unsubstituted.

16. A compound of formula (III) according to claim 15 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally subsituted with one or more subsitutents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted withhalogen; R^7 is C_{1-8} alkyl, optionally subsituted with one or more substituents selected from the group consisting of hydroxy; $-NH_2$; or heterocycle; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle which may be optionally substitued with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cylcoalkyl;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-oxo-1lambda~4~,4-thiazinan-4-yl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]acetamide;

2-[2-(1-benzofuran-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-phenylacetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-furoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

2-{4-chloro-2-[3-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(3-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(3-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-[4-chloro-2-(3-methylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(1-methyl-1H-imidazol-2-yl)carbonyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{2-[3,5-bis(trifluoromethyl)benzoyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(6-methyl-1,3-benzothiazol-5-yl)acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfonyl]benzoyl}phenoxy)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-thiazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-oxazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{4-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(2-methyl-4-{3-[(methylamino)sulfonyl]propoxy}phenyl)acetamide;

30. A compound selected from the group consisting of compound number 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, and 433.